#7 4/26-27/1991

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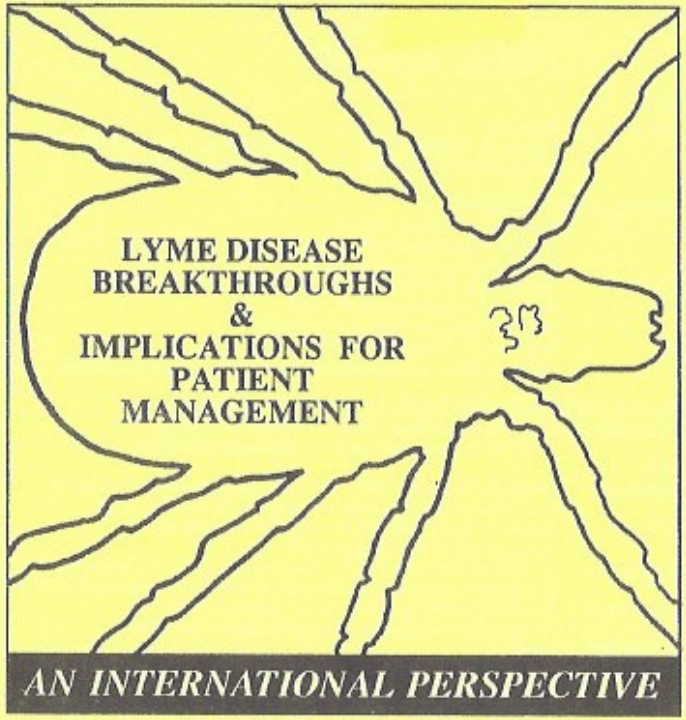

AN INTERNATIONAL PERSPECTIVE

APRIL 26 & 27, 1991

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HEALTH OFFICIALS.

Friday, April 26

AM

8:00-8:10 *Welcome*
James N. Miller, PhD *UCLA School of Medicine*
Michael A. Lovett, MD, PhD *UCLA School of Medicine*

RESEARCH FUNDING

8:10-8:20 *The LBF FUNDING PLANS*
Karen Vanderhoof-Forschner, BS, MBA, CPCU, CLU
Chair, Board of Directors, LBF

8:20-8:45 *NATIONAL INSTITUTES OF HEALTH - 1991 FUNDING*
Robert L. Quackenbush, PhD
Program Officer of Bacteriology, NIAID
Stephen P. Heyse, PhD, MD
Director, Office of Prevention, Epidemiology, & Clinical, NIAMS

PATHOGENESIS AND LABORATORY DIAGNOSIS

Co-Moderators: **James N. Miller, PhD** *UCLA School of Medicine*; **Bettina Wilske, MD** *Max von Pettenkofer Institut*

AM

8:50-9:10 **Jorge L. Benach, PhD** *New York State Department of Health*
The Inflammatory Response and Phagocyte Interaction in LB

9:15-9:35 **Marc G. Golightly, PhD** *SUNY at StonyBrook*
Humoral and CMI Responses in LB

9:40-10:00 **D. Denee Thomas, PhD** *Bowman Gray School of Medicine, NC*
Comparative Adherence and Invasion among the Pathogenic Spirochetes

10:05-10:25 **David R. Blanco, PhD** *UCLA School of Medicine*
Comparative Pathogenesis among Pathogenic Spirochetes

10:30-10:45 *Break*

10:45-11:20 **Paul H. Duray, MD** *Fox Chase Cancer Center, PA*
The Pathology of LB

11:25-11:50 **Bettina Wilske, MD** *Max von Pettenkofer Institut, Germany*
Problems and Possible Improvements in Serodiagnosis of Lyme Borreliosis

11:55-12:15 **Thomas J. White, PhD** *Roche Diagnostics Systems, CA*
PCR in the Diagnosis of LB

MOLECULAR & CELLULAR BIOLOGY OF *B. BURGDORFERI*

Moderator: **Michael A. Lovett, MD, PhD** *UCLA School of Medicine*

PM

1:05-1:30 **Bettina Wilske, MD** *Max Von Pettenkofer Institut, Germany*
Antigenic Diversity and Variability Among Different Strains

1:35-2:00 **Robert G. Cluss, PhD** *Department of Biological Sciences, CA*
Heat Shock Proteins of *B. burgdorferi*

2:05-2:35 **Claude F. Garon, PhD** *Rocky Mountain Laboratories, MT*
Plasmid Associated and Species Specific DNA Sequences in *B. burgdorferi*

2:40-3:05 **Tom G. Schwan, PhD** *Rocky Mountain Laboratories, MT*
Plasmid Profiles and Changes in Infectivity

3:10-3:25 *Break*

3:25-3:45 **Nyles W. Charon, PhD** *W. Virginia University Medical Center*
Comparative Molecular and Cellular Biology among Pathogenic Spirochetes

EXPERIMENTAL ANIMAL MODELS & VACCINES

Moderator: **Edward M. Schneider, PhD** *Veterinary Research Associates, NY*

PM

3:50-4:10 **Stephen Barthold, DVM, PhD** *Yale University, CT*
Rodent Models

4:15-4:35 **Ronald F. Schell, PhD** *University of Wisconsin*
The Hamster Model

4:40-5:00 **Edward M. Bosler, PhD** *New York State Department of Health*
The Canine Model

5:05-5:25 **Russell C. Johnson, PhD** *University of Minnesota*
Experimental LB Vaccines

6:00-7:30 *Reception and Networking*

7:30-9:30 *Awards Dinner, By Reservation*

Saturday, April 27

CLINICAL MANIFESTATIONS, DIAGNOSIS, & TREATMENT I

Moderator: **Gerold Stanek, MD** *Hygiene Institute der Universitat Wein, Austria*

AM

8:00-8:20 **R. J. Scrimenti, MD** *Columbia, St. Mary's Hosps., WI*
Early Manifestations and Treatment of LB

8:25-8:45 **Paul E. Lavoie, MD** *University of California Medical School*
Arthritic Manifestations and Treatment of LB

8:50-9:20 **Rudolf Ackermann, MD** *University of Köln, Neurology, Germany*
Neurological Manifestations and Treatment of LB

9:25-9:55 **Gerold Stanek, MD** *Hygiene Institute der Universitat Wein, Austria*
Cardiac Manifestations and Treatment of LB

10:00-10:20 **Robert L. Lesser, MD** *Yale University School of Medicine, CT*
Ophthalmologic Manifestations and Treatment of LB

10:25-10:40 *Break*

CLINICAL MANIFESTATIONS, DIAGNOSIS, & TREATMENT II

Moderator: **Paul E. Lavoie, MD** *University of California, San Francisco*

AM

10:40-11:00 **James Katzel, MD** *Mendocino Health Group, CA*
The Real World of Primary Care

11:05-11:35 **Alan McDonald, MD** *Southampton Hospital, NY*
Lyme Disease in the Gestational Period

11:40-11:59 **Paul E. Lavoie, MD** *University of California Medical School*
Chronic Relapsing Fever Borreliosis

ECOLOGY

Co-Moderators: **Robert S. Lane, PhD** *University of California*; **Willy Burgdorfer, PhD, MD (hon)** *Rocky Mountain Laboratories*

PM

1:10-1:30 **Robert Murray, PhD** *California Department of Health Services*
Geographical Distribution, Prevention, and Control

1:35-1:55 **John F. Anderson, PhD** *CT Agricultural Experiment Station*
Epizootiology in Eastern U.S.

2:00-2:20 **Robert S. Lane, PhD** *University of California, Berkeley*
Epizootiology in Western and Southwestern U.S.

2:25-2:45 **Willy Burgdorfer, PhD, MD (hon)** *R.M.L., MT*
Epizootiology in Europe

2:50-3:20 **David H. Persing, MD, PhD** *The Mayo Clinic*
The Antiquity of *B. burdorferi*, over 45 years in the USA

3:25-3:40 *Break*

3:45-4:15 **Ralph A. Barr, PhD** *UCLA School of Public Health*
Non-tick LB Transmission Potential

4:20-4:50 **John E. Madigan, DVM** *University of California, Davis*
Veterinary Aspects of LB

5:00 **Karen Vanderhoof-Forschner** *Lyme Borreliosis Foundation*
Closing Remarks

7:00-8:00 *Public Forum*

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Pediatr Infect Dis J, 7:286-289, 1988
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Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy

KLAUS WEBER, MD, HANS-JÜRGEN BRATZKE, MD, UWE NEUBERT, MD, BETTINA WILSKE, MD, AND PAUL HARRISON DURAY, MD

Lyme borreliosis (LB) is a spirochetosis which, like syphilis, develops in three stages: erythema migrans, constitutional symptoms and/or lymphocytoma (Stage 1); carditis, early neurologic involvement and/or musculoskeletal symptoms (Stage 2); and arthritis, acrodermatitis chronica atrophicans and/or chronic encephalitis as part of Stage 3.[1,2] The causative agent of LB is *Borrelia burgdorferi*.[3]

Spirochetes have been identified morphologically in spleen, renal tubules and bone marrow in a newborn having died of cardiac abnormalities[4] and in heart, liver, adrenal gland and brain of a stillborn.[5] In addition, *B. burgdorferi* has been cultured from fetal liver.[6] The mothers of these infants did not receive antimicrobial therapy during pregnancy.

We now demonstrate *B. burgdorferi* in the brain and liver of a newborn whose mother had been treated with oral penicillin for LB during the first trimester of pregnancy.

CASE REPORT

In the course of a prospective study carried out since 1978,[6,7] we encountered a 37-year-old woman who was bitten by several ticks near Würzburg, Germany, in late July, 1984, during the second month of her first pregnancy. Two weeks later she observed an expanding itchy skin lesion on the left lower leg around one of the tick bites. An erythema migrans about 8 cm in diameter was noted when she attended the private office of one of us (KW) on August 13, 1984. According to a questionnaire there were no associated symptoms before, during and up to 2 years after the first visit. A mild form of erythema migrans disease, the European form of LB,[6,7] was diagnosed. The woman received 1 milli-IU propicillin (an oral penicillin similar in its action to phenoxymethylpenicillin) 3 times daily for a week. On August 20 the erythema migrans had disappeared. IgM and IgG antibody titers against *B. burgdorferi* were negative (<1:16) in an indirect immunofluorescence test on August 13 and October 23, 1984 (method as in Reference 8); however, reexamination of the sera when other tests were available a few years later yielded a significant rise of antibody titers against *B. burgdorferi* in the IgM enzyme-linked immunosorbent assay (ELISA) from <6.25 units/ml (normal range, up to 25 units/ml) on August 13 to 37.7 units/ml on October 23 and in the indirect hemagglutination test from 1:80 (negative) to 1:640 (positive) whereas the IgG ELISA remained negative (methods as in References 9 and 10). Follow-up revealed that the woman had delivered a normal appearing child on March 10, 1985, after an uneventful pregnancy. Delivery was aided by vacuum extraction. Twenty-three hours after birth the child suddenly developed difficulty in breathing and succumbed within half an hour. A resuscitation attempt was unsuccessful.

Postmortem examination showed a well-proportioned newborn with a weight of 3400 g and a length of 51 cm. On the right side of the scalp was a large swollen and hemorrhagic area, but there was no skull fracture. The brain showed no bleeding or rupture other than a small infratentorial hemorrhage. In the tentorium and falx cerebri, a few small hemorrhages were discovered. Microscopically there were cerebral and cerebellar edema and congestion. No significant inflammation was found in any organ including heart, liver, brain and kidney (placenta and spleen were not available). An immunohistologic examination of cerebral tissue and matrix of the brain for the common leukocyte antigen yielded negative results (courtesy of Dr. W. Permanetter, Department of Pathology, University of Munich). A small perivenous hemorrhage with minor aggregates of leukocytes was detected in the pons. The lungs showed extreme congestion, microscopic edema and a small amount of amniotic fluid without inflammatory signs. The cardiovascular system showed no malformations. The death of the newborn was probably due to a respiratory failure as a consequence of perinatal brain damage. Modified Dieterle[11] or modified Warthin-Starry[12] silver stains applied to paraffin sections of all available organs of the infant showed a few spirochetes strongly resembling *B. burgdorferi* in the brain (Fig. 1) and liver (Fig. 2). With an avidin-biotin method utilizing three chromogen substrates (diaminobenzidine and alkaline phosphatase chromogens I and III), *B. burgdorferi* was identified in rare paraffin sections of the brain when the monoclonal antibody H 5332 directed against outer surface protein of this organism (kindly supplied by Dr. A. G. Barbour, University of Texas, San Antonio; Fig. 3) was used.

On December 5, 1986, the mother had negative, indirect hemagglutination (1:160), IgG and IgM (14.7 units/ml) ELISA and indirect immunofluorescence tests (IgM and IgG type antibodies) and a negative *Treponema pallidium* hemagglutination. She delivered a second child on February 24, 1986, after an uneventful pregnancy. Serologic examination of this healthy infant at the age of 11 months yielded negative indirect hemagglutination and immunofluorescence tests (IgM and IgG type antibodies) and a negative IgM and IgG ELISA.

DISCUSSION

We have found *B. burgdorferi* in human neonatal brain and liver although the mother had been treated

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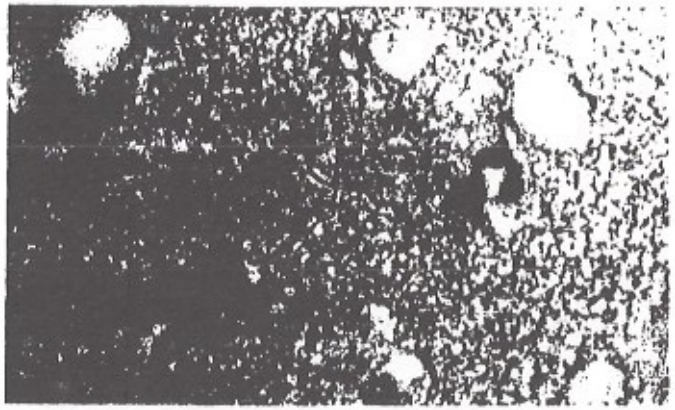

FIG. 1. Photomicrograph of brain showing a single, elongate spirochete in an extracellular position. The thickened blunt end is an effect of duplication that can be seen in cell cultures of *B. burgdorferi*. Dieterle stain, × 1250.

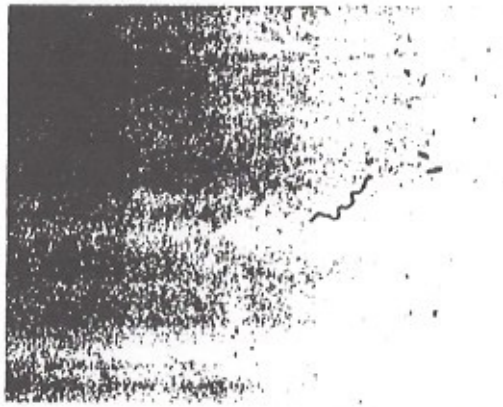

FIG. 2. This spirochete observed in the lumen of a large hepatic vein has the typical morphology of *B. burgdorferi*. Modified Warthin-Starry stain, × 1300.

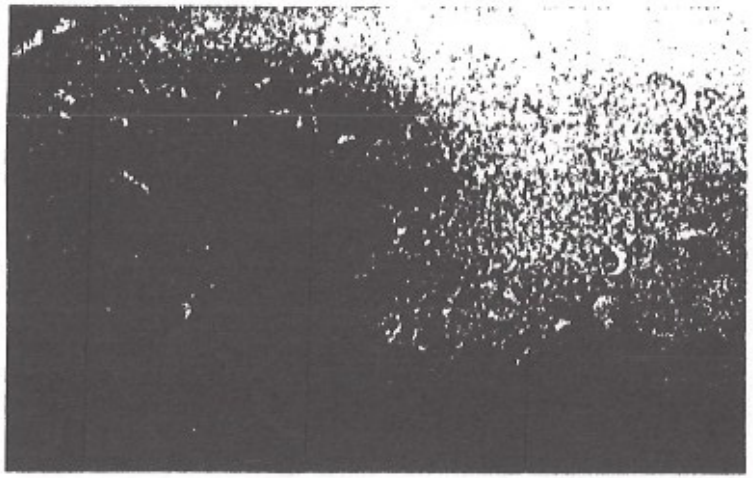

FIG. 3. *B. burgdorferi* is seen in the middle of a section of the brain. Immunostain with monoclonal anti-outer surface protein using diaminobenzidine as the chromogen and no counterstain. × 500.

with an orally administered penicillin for LB during early pregnancy.

The morphology of the spirochetes as seen by silver stain was consistent with our previous experience with *B. burgdorferi* in tissue sections.[4,11,12] Application of an immunohistochemical method allowed us to identify the spirochetes as *B. burgdorferi*.

The fact that *B. burgdorferi* can exist within human brain (Reference 5 and our case) might be important for the discussion of the pathogenesis of the recently recognized encephalitis of tertiary LB. This late type of encephalitis has thus far been based only on clinical and serologic evidence.[13,14] Interestingly, *B. burgdorferi* has recently been isolated from brain of Syrian hamsters.[15]

In our case and in two other cases of congenital LB[4,5] there was no significant inflammation in any organ examined. In erythema migrans, a hallmark of LB,[1,6,7] the presence of *B. burgdorferi* is associated with an accumulation of inflammatory cells.[12,16] However, 5 of 7 experimentally infected hamsters showed no significant inflammation in any major organ system besides lymphoid hyperplasia in the spleen, although *B. burgdorferi* could be isolated from spleen, kidney and eye of all animals.[17] The reason for the lack of inflammation remains open to speculation.

Orally administered penicillin sufficient to clear the erythema migrans of the mother was apparently not curative for our child. There have been several reports describing more severe later manifestations such as meningitis, arthritis or carditis in patients having received oral penicillin for early disease.[18,19] In the first of these reports[18] the ensuing meningitis has been treated successfully with high doses of parenteral penicillin, now the favored antibiotic treatment for neurologic involvement.[20]

We conclude that orally administered penicillin for Lyme borreliosis during pregnancy does not seem to be sufficient to prevent infection of the child. Thus we now tentatively recommend intravenous penicillin, 6 milli-IU four times daily for 10 to 14 days in pregnant women with LB. In patients allergic to penicillin, erythromycin, 500 mg four times daily, might be an alternative but experience with this regimen is limited[21] and a dosage of 250 mg four times daily has not given satisfactory results.[19]

ACKNOWLEDGMENTS

We are indebted to Drs. A. G. Barbour, W. Permanetter, W. Nützel (dermatologist, Munich) and Frau U. Perschau for their contributions.

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1989

Gestational Lyme Borreliosis
Implications for the Fetus

Alan B. MacDonald, MD

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LYME DISEASE

Russell C. Johnson, PhD, *Guest Editor*

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Gestational Lyme Borreliosis

Implications for the Fetus

*Alan B. MacDonald, MD**

Fetal death, malformation, or retarded development are the most feared potential consequences of intrauterine infection. Some cases of active Lyme borreliosis (LB) in pregnancy have been circumstantially linked to adverse pregnancy outcomes.[3-5,7,9] The majority of women, however, appear to have normal infants in spite of the documentation of Lyme borreliosis during their pregnancies. Epidemiologic studies have attempted to estimate the risk that LB may pose to the fetus. This article will review the epidemiologic evidence and will add the perspectives of the serologist and pathologist. LB in pregnancy is twice the diagnostic problem for the physician, because two patients are simultaneously at risk for tissue injury. The complex spectrum of clinical manifestations of LB in the mother is complementary to an equally complex array of signs and symptoms of prenatal LB in the fetus and infant.

EPIDEMIOLOGY STUDIES

A 9-year retrospective study of 19 cases of clinically active Lyme disease in pregnant women was completed in 1986 in a joint venture between The Centers for Disease Control and the Yale University School of Medicine.[6] "Only cases in which the outcome of pregnancy was not known were enrolled in the study." In the same time period (1975 to 1985), more than 700 patients with Lyme disease were evaluated at the Yale University School of Medicine. It is uncertain why the patients who were entered into the prospective study did not include all women who developed Lyme disease while they were pregnant, irrespective of the outcome of their pregnancy. Erythema migrans, the pathognomonic cutaneous lesion of LB was identified in 17 women. Two women without EM were included in the study. These patients presented with facial palsy and arthritis (without serologic evidence) and with arthritis and reactive serology.

* Attending Pathologist, Southampton Hospital, Southampton, New York

One fetal death at 20 weeks gestation occurred in a woman with erythema migrans in the sixth week of her pregnancy followed by meningitis in the seventh week, and arthritis in the sixteenth week. An autopsy of the fetus disclosed no congenital malformations, no inflammatory infiltrates in fetal tissues, and no evidence of spirochetes by culture or histologic methods. A second infant developed cortical blindness at 8 months of age. His mother had erythema migrans in week 27 of pregnancy and was treated with oral penicillin for 10 days. The infant is now 3 years old and has persistent learning disability due to cortical blindness. Three additional adverse outcomes in this cohort included one case each of prematurity with hyperbilirubinemia without kernicterus, syndactyly of the second and third toes, and self-limited hyperbilirubinemia with a concurrent generalized petechial and vesicular rash in a full-term infant.

The epidemiologist's summation observations included the following: (1) one second-trimester abortion was not expected to occur by chance in a group of 19 pregnancies and therefore was an important finding; (2) a case of cortical blindness and developmental delay could not be linked to maternal infection; (3) no two adverse outcomes were similar and therefore a link between Lyme disease and adverse fetal outcome could not be proven; and (4) the frequency of adverse outcomes prompted a consensus recommendation that immediate penicillin therapy be instituted for pregnant women who develop Lyme disease.

SEROLOGY STUDIES

The CDC-Yale Study of Lyme disease in pregnancy did not have serology data for each of the patients. Patients were diagnosed with Lyme disease based on the erythema migrans lesion. Seroconversion is expected in only 40 to 60 per cent of patients after the EM lesion is identified. Examination of umbilical cord blood specimens from five clinically normal infants showed no evidence of detectable antibodies to BB. The authors concluded, based on the seronegative status of the five infants, that "there was no evidence of occult infection." (A single negative serologic result from umbilical cord blood certainly does not exclude LB, especially in light of the recent documentation of a seronegative state in certain patients with chronic disease[8] and in light of the observations of Stokes in prenatal syphilis. A sixth infant's umbilical cord blood specimen was positive for antibodies to BB, but 7 months later the infant was seronegative. The authors did not indicate whether this infant's antibodies were of the IgM class (indicating intrauterine infection) and did not state whether they believed that this infant had an occult infection which might have reverted to a seronegative state as a result of antibiotic therapy.

Williams and colleagues[11] conducted a prospective study of newborn infants to determine whether clinical and serologic differences could be detected between babies whose mothers had resided in an endemic area for LB versus those whose mothers resided in a nonendemic area for LB. In 255 infant cord blood specimens from an endemic

area, 10.2 per cent had some detectable antibody to BB and in 166 from a nonendemic area 2.4 per cent showed detectable antibodies to BB in umbilical cord blood. Major congenital malformations were not significantly different between the two groups, but low birth weight and neonatal jaundice were more often observed in babies in the endemic area. None of the observed parameters were statistically different between infants in the two groups.

A conspicuous absence of fetal deaths or miscarriages in the Williams patient study group is an inevitable consequence of the selection process in this study. Only live born infants were included. The opportunity to observe congenital anomalies associated with miscarriages, stillbirth, or perinatal infant death was not permitted due to the design of the study. Therefore, the author's conclusion that no association can be supported between gestational LB and congenital malformation should be a highly qualified statement with multiple disclaimers.

PATHOLOGY STUDIES

Schlesinger et al[7] proved in their 1985 report that BB could be vertically transmitted to the fetus. Spirochetal fragments were identified by silver impregnation techniques in autopsy fetal spleen, kidney, and bone marrow. The immediate cause of neonatal death at 39 hours after delivery was cardiac failure secondary to the hypoplastic left heart complex of anomalies. Although the Schlesinger report stated that BB was not found in the fetal myocardium, MacDonald subsequently succeeded in demonstrating BB in the myocardium from the Schlesinger case using an immunohistochemical technique (Fig. 1). MacDonald[4,5] reported four additional cases of maternal fetal transmission of BB with cardiac anomalies in three of the fetuses. Spirochetes were seen on darkfield examination of fetal livers in all cases and histopathology studies confirmed that spirochetes were present in various fetal and placenta tissues in all cases. Weber and colleagues[9] described transplacental transmission of BB followed by neonatal infant death in a case from Germany. Spirochetes were found in the brain and liver at autopsy despite the fact that the mother had taken penicillin promptly after the erythema migrans lesion appeared in the second trimester of her pregnancy. Lavoie and colleagues[3] reported a full-term neonatal death due to aortic thrombosis in which BB was cultured from the infant's brain. Spirochetes were not identified in fetal tissues by histologic methods. Table 1 abstracts various parameters from these autopsy cases.

ANALYSIS—HISTOPATHOLOGY STUDIES OF GESTATIONAL LB

Autopsy evidence for gestational LB establish that spirochetes are in fetal or placental tissue. Such cases show that serological evidence is often lacking when maternal blood is tested for antibodies to BB immediately after the delivery of a living or dead fetus. Routine tissue studies

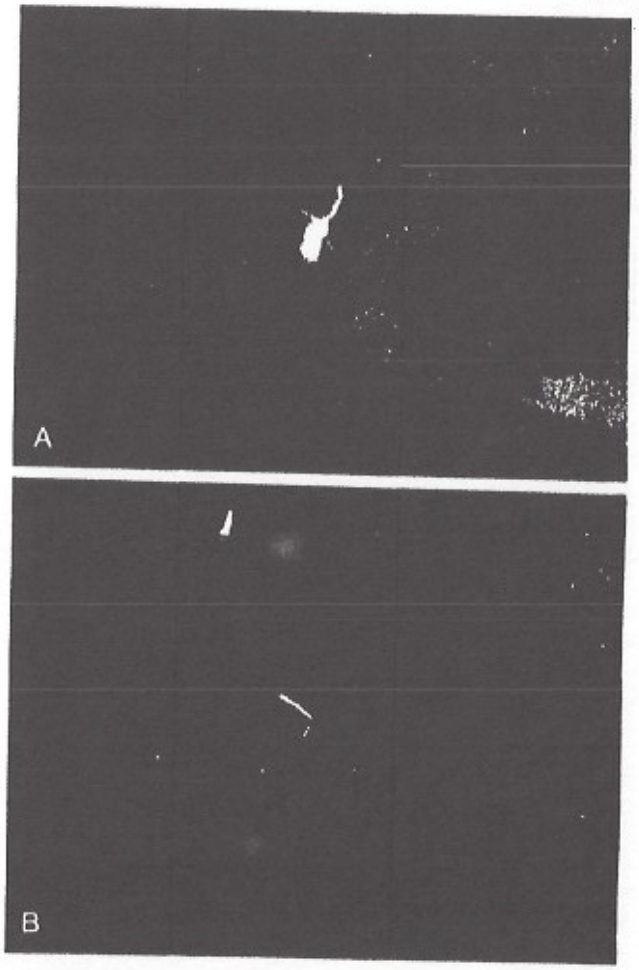

Figure 1. *A, B. burgdorferi* in fetal autopsy myocardium. Indirect immunofluorescence, 1000× magnification.[7] *B, B. burgdorferi*, reference strain B31 in agarose. Indirect immunofluorescence, 1000× magnification.

with ordinary microscopic techniques, namely hematoxylin and eosin stained sections, fail to provide clues that infection has reached the fetus because none of the autopsies to date has shown inflammation in the tissues which contained BB. In each of the previously published cases, a strong index of suspicion was the sole cause for the intricate and exhaustive medical investigation specifically directed toward the subtle clinical

Table 1. *Clinical Parameters from Autopsy Cases*

CITATION	EM LESION	MATERNAL SEROLOGY	TISSUE INFLAMMATION	TISSUE SPIROCHETE	CARDIAC FETAL ANOMALY
Schlesinger	+	—*	−	+	+HLC‖
Case 1	+	+	−	+	+VSD‖
Case 2	−	−	−	+	+ASD‖
Case 3	−	−	−	+	+CA¶
Case 4	−	−	−	+	−
Weber	+	—†	−	+	−
Lavoie	−	−	−	−	−

* IFA titer of 1/128 is not significant by 1989 CDC criteria for case definition of Lyme borreliosis.
† Initial Lyme serology in 1985 is negative by IFA and ELISA; repeat testing on frozen serum 3 years later were positive.
‖ Hypoplastic left heart complex of malformations.
‡ Ventriculoseptal defect of the atrioventricular type.
‖ Atrial septal defect of the ostium primum type.
¶ Coarctation of the aorta; infantile type.

and histopathologic evidence of LB and its spirochetal agent BB. Patience and diligence are required if the histopathologist is to succeed in visualizing BB with oil immersion magnification. There are many potential pitfalls and there are many opportunities to fail when looking for the spirochete.

LEVELS OF PROOF OF ACTIVE LYME BORRELIOSIS

Three perspectives—epidemiology, serology, and histopathology—offer nonconvergent views of the potential impact of LB on human pregnancy. Nonconvergence tends to interfere with clear vision and clear thought. The serologist's tools for antibody detection have technical, biologic, and epistemologic shortcomings. False positive and false negative results are menacing problems that perplex the diagnostician.[1] If false results are to be feared, it is the false negative result which holds the greatest peril for the patient. Under the best of circumstances, as noted in the CDC report of Lyme disease in pregnancy, "results of serological tests for Lyme disease are often negative during the first several weeks of infection."[6] From a biologic perspective, most of the fatal cases of LB in pregnancy were reactive either in titers in the borderline region or were completely nonreactive in serologic tests. The tendency toward seronegativity in pregnancy makes maternal serology a less satisfactory discriminator of maternal infection and useless as a practical tool to predict the actual state of the fetus (unless the patient and physician are willing to accept the hazard of direct sampling of fetal blood while the fetus is still in utero). Erythema migrans is a pathognomonic tool which is exploited by the epidemiologists to diagnose active early Lyme borreliosis.

It is estimated that one half of patients with LB never develop the erythema migrans lesion. Furthermore, erythema migrans in the mother does not predict whether the infection will remain localized to the skin or whether the infection may have already entered the bloodstream and pose a threat to the health of the fetus. There is no placental protection or barrier that protects the fetus from the spirochete once the microbe has entered the maternal bloodstream. Therefore, if we seek the truth, we must seek the spirochete directly by pathologic study of available tissues from the products of conception.

TWO PATIENTS SIMULTANEOUSLY AT RISK: A DOCTOR'S DIAGNOSTIC DILEMMA

LB in the pregnant patient simultaneously involves two patients, the mother and her fetus. The indirect nature of the diagnostic process regarding the presence of disease, its activity, its potential severity, and its response of appropriate antibiotic therapy are uncertain for the mother, and far more difficult for the fetus. Theoretical possibilities are presented in Table 2.

A CONCEPTUAL MODEL OF PRENATAL SYPHILIS

The clinical diversity of LB is a formidable diagnostic challenge to the physician which is matched by the labyrinthine complexity of prenatal syphilis. Three quintessential paradigms from the literature of congenital syphilis appeared in the textbook by Stokes in 1945:[8]

1. "Prenatal syphilis is a collection of rare events of interest to the connoisseur of the elegant art of medical investigative diagnosis."
2. "The diagnosis of syphilis in a dead fetus is just as difficult as the diagnosis of syphilis in a living fetus."
3. "Never 'always,' Never 'never.'"

Additional wisdom from 400 years of cumulative observation of syphilis with special emphasis on the situation of pregnancy is abstracted in Table

Table 2. *Potential Situations of Gestational Lyme Borreliosis*

MOTHER	FETUS	CASE NUMBER
Clinical disease	No disease	14
Subclinical disease	Active disease	4–12
Clinical disease	Clinical disease	1
Effects of Antibiotic Therapy: Mother Versus Fetus		
Antibiotic cure	Antibiotic cure	12, 14
Failure	Failure	—*
Cure	Failure	Weber, 13
Failure	Cure	—*

* No published cases for these categories.

Table 3. *Vignettes from Clinical Observation of Prenatal Syphilis*

"Seronegative results are absolutely untrustworthy."
"The exact date of maternal or fetal infection is often impossible to determine."
"Asymptomatic seronegative mothers may bear syphilitic children."
"Prenatal syphilis may only appear as a tardive manifestation in the child after birth."
"Repeated unsuccessful pregnancy (miscarriage or stillbirth) has a high value as a diagnostic clue to maternal syphilis."

3. The diversity of prenatal syphilis at the clinical level is illustrated below and the laboratory diversity of prenatal syphilis is presented in Table 4 (note that approximately 20 per cent of infants who acquired syphilis in utero were seronegative at birth).

The manifestations of heredosyphilis in newborn babies include: eruptive cutaneous lesions; snuffles; irritability; fissured lips; pseudoparalysis of Parrot; anemia; mucous patch; anal condyloma lata; aphonic cry; marasmus; nephritis; icterus neonatorum; and no clinical symptoms detectable at delivery.

Tardive manifestations of prenatal syphilis that are not apparent at birth, but develop in childhood or adolescence include: Hutchinson incisor; scaphoid scapula; interstitial keratitis; eighth nerve deafness; saddle nose; hydroarthrosis of Clutton; optic atrophy; and hydrocephalus.

THE SOUTHAMPTON HOSPITAL FETAL BORRELIOSIS STUDY

Southampton Hospital is a 192-bed community hospital serving the eastern end of Suffolk County, a coastal region of Long Island in New York State. Between 650 and 750 babies are delivered each year by the hospital's obstetric staff. Lyme borreliosis is hyperendemic in Suffolk County and the yearly LB infection rates have consistently been among the highest in the United States since 1982 when the New York State Department of Health began its surveillance program. High rates of infection predict that the insect vector, *Ixodes dammini*, is ubiquitous in our communities and that the percentage of ticks carrying the spirochete is high in the communities served by the hospital. Medical entomologists

Table 4. *Prenatal Syphilis: Serial Studies of the Mother and Child*

TYPE	SEROLOGY OF SYPHILIC MOTHER	INFANT'S SEROLOGY AT BIRTH	ULTIMATE SYPHILIS STATUS OF CHILD	NUMBER OF CASES	PERCENTAGE TOTAL
1	+	+	+	36	12
2	+	−	+	54	18
3	−	−	+	35	4
4	−	+	+	1	0.3
5	+	+	−	25	8
6	+	−	−	101	35.7
7	−	−	−	72	24

have demonstrated that between 60 and 100 per cent of Ixodid ticks carry the infection, depending on the tick habitats sampled and the time of the year that the ticks are collected. (Our medical community includes Shelter Island, New York, which is Dr. William Burgdorfer's source of the Ixodid ticks from which he identified "Borrelia burgdorferi in 1981). The extraordinary interest in Lyme borreliosis in pregnancy at Southampton Hospital is in part due to the opportunity to see various manifestations of the infection which our ecosystem presents and which may not yet exist in other areas.

A 7-year retrospective analysis of perinatal autopsies performed from 1978 to 1985 (Table 5) and a 3-year prospective study of perinatal deaths from 1985 to 1988 has yielded evidence that *Borrelia burgdorferi* is detectable in some perinatal autopsy tissues.

Case 1: Fetal Lyme Borreliosis with Ventriculoseptal Defect

A 24-year-old white woman was admitted in February 1985 in labor at term of her pregnancy. Ultrasound examination showed that the fetus was dead when she arrived at the hospital. Following the delivery of her stillborn infant and completion of the fetal autopsy, a retrospective interview established that she had acquired Lyme borreliosis in the first trimester of her pregnancy outside of Salt Lake City, Utah. Postpartum serologic studies yielded conflicting results because the Centers for Disease Control found strongly reactive results by IFA and ELISA, as did the New York State Department of Health; however, the Yale University laboratory of Dr. Allen Steere could detect no evidence of specific antibodies for *B. burgdorferi*. Fetal viscera showed *B. burgdorferi* in the liver, adrenal, brain, heart, and placenta. Spirochetes were seen by darkfield examination of fetal liver and these bound specific monoclonal antibody H5332. No microscopic inflammation was identified in tissue sections which contained the spirochete (Fig. 2). Points to emphasize from this case are: (1) lack of tissue inflammation in infected tissues; (2)

Table 5. *Tabulation of Southampton Hospital Perinatal Autopsies 1978–1988*

Total autopsies		24
Autopsis showing evidence of Lyme borreliosis		4
Autopsy diagnosis		
Group I (no evidence of gestational LB N = 20)		
Abruptio placenta	4	
B 19 Parvo virus	1	
Prune belly syndrome	1	
Thanatomorphic dwarf	1	
Crouzon disease	1	
Bilateral renal agensis	2	
Stillborn (cause unknown; no cardiac anomalies seen)	10	
Group II (evidence of gestational LB n = 4)		
Ventriculoseptal defect (AV canal type)	1	
Ventriculoseptal defect (unspecified type)	3	
Neural tube defects (hydrocephalus and meningomyelocoele)		1
Absence of left hemidiaphragm		1

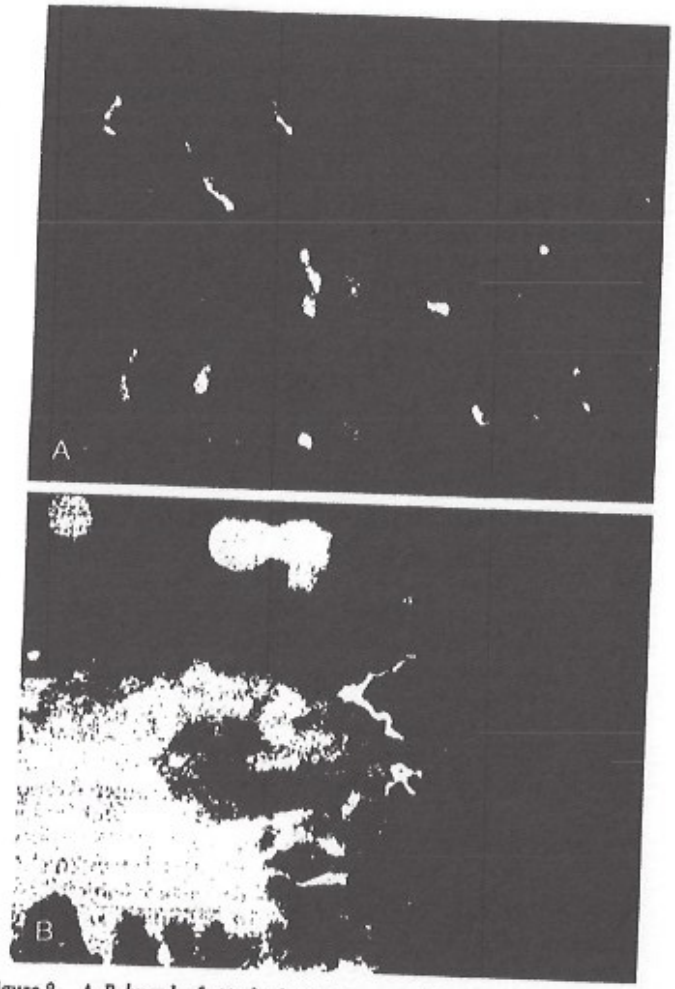

Figure 2. *A, B. burgdorferi* in fetal autopsy myocardium (Case 1). Indirect immunofluorescence, 1000× original magnification. *B, B. burgdorferi* in fetal autopsy adrenal gland (Case 1). Indirect immunofluorescence, 1500× original magnification.

discrepancy in serology testing; (3) positive cultures of spirochetes from fetal liver; (4) concurrence of first trimester infection with events of cardiac organogenesis and subsequent identification of a ventriculoseptal defect; (5) intrauterine fetal growth retardation; and (6) acquisition of infection in a "nonendemic area" and identification of infection by entirely retrospective analysis.

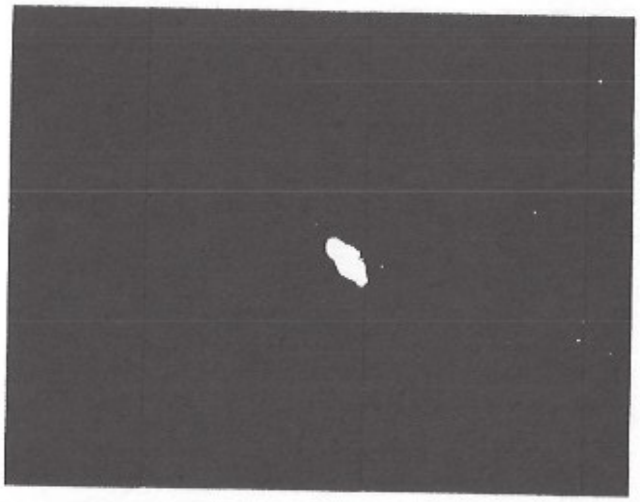

Figure 3. *B. burgdorferi* in fetal placenta. Indirect immunofluorescence, 1000× original magnification.

Case 2: Fetal Lyme Borreliosis with Miscarriage at 19 Weeks Gestation

A 22-year-old white woman became pregnant while residing on a farm in Suffolk County, New York. She recalled no tick bite and did not see an erythematous skin lesion. Severe toxemia of pregnancy in week 17 of pregnancy was marked by hypertension, facial edema, and albuminuria and peripheral edema. A macerated 514 gm stillborn female fetus with an atrial septal defect was delivered in week 19. Postpartum maternal blood showed negative results in two laboratories for specific antibodies to *B. burgdorferi*. *B. burgdorferi* was identified in tissue by indirect immunofluorescence (Fig. 3).

Case 3: Fetal Lyme Borreliosis with Miscarriage at 23 Weeks Gestation

A 37-year-old white woman became pregnant while residing on Shelter Island, New York. Fetal and maternal health appeared normal through week 20 of gestation. An amniocentesis at week 20 showed a normal fetal karyotype. Toxemia of pregnancy began in week 22 with hypertension and proteinuria. In week 23 a 490 gm stillborn male fetus was delivered. The mother's medical history was remarkable for an undifferentiated collagen vascular disorder which was in sustained clinical remission while she was pregnant, but which reactivated after she lost the fetus. A postpartum Lyme serology test was nonreactive in two laboratories, but an FTA-ABS test for syphilis was reactive at an unstated dilution and was interpreted as a biologic false positive result reflecting her collagen disease. A fetal autopsy showed coarctation of the aorta and no inflammation of fetal viscera in spite of visceral spirochetosis. *B.*

burgdorferi was identified in tissue by indirect immunofluorescence (Fig. 4).

Case 4: Fetal Lyme Borreliosis with Miscarriage at 15 Weeks Gestation

A 32-year-old Oriental woman became pregnant while residing in East Hampton, New York. Her course was uneventful in the first trimester of her pregnancy. She miscarried at 15 weeks gestation and delivered an 85 gm female fetus with no congenital anomalies. Spirochetes were observed in the fetal liver and in the placenta, but no inflammation was found in fetal viscera. Postpartum maternal serology was negative for specific antibodies to BB. *B. burgdorferi* was identified in tissue by indirect immunofluorescence.

Case 5: Fetal Lyme Borreliosis in Term Delivery and Postnatal Death After 4 Hours

A 25-year-old black woman presented in September 1978 in labor in week 39 of pregnancy. Her antepartum course was remarkable only for a brief episode of vaginal bleeding in her second month of pregnancy. A 2250 gm female infant showed multiple anomalies at delivery including hydrocephalus, omphalocoele, clubfoot, spina bifida, and meningomyelocoele. Respiratory distress developed in the newborn nursery and 4 hours later the infant died. Autopsy disclosed a large ventriculoseptal defect as an additional malformation. Spirochetes were identified by immunohistochemistry in a retrospective examination of fetal autopsy tissue.

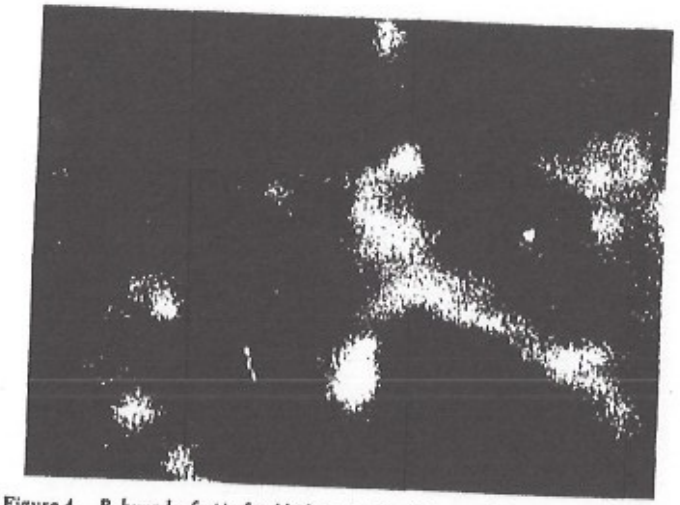

Figure 4. *B. burgdorferi* in fetal kidney. Indirect immunofluorescence, 1500× original magnification.

Case 6: Fetal Borreliosis, Term Pregnancy, With Postnatal Death at 30 Minutes

A 33-year-old white woman was admitted in February 1979 in week 40 of pregnancy. Her antepartum course was remarkable for uterine growth retardation as detected in serial obstetrical ultrasound examinations. A 1950-gm female infant showed poor color and poor respiratory activity at birth. The infant showed profound bradycardia with heart rates of less than 60 beats per minute, with progressive decline in cardiac output and death 30 minutes after birth despite maximum support in the neonatal nursery. Autopsy disclosed a large (1 cm diameter) ventriculoseptal defect and showed an absence of the left hemidiaphragm with herniation of abdominal viscera into the left hemithorax. Spirochetal fragments were identified by indirect immunofluorescence in a retrospective examination of fetal autopsy tissue.

Case 7: Fetal Lyme Borreliosis with Miscarriage at 17 Weeks Gestation

A 34-year-old black woman was admitted in March 1986 in week 17 of her third pregnancy. She delivered a 30 gm male fetus in the emergency room. In the 2 weeks prior to admission, she had experienced vaginal bleeding and abdominal cramping. An obstetric ultrasound examination in week 12 of pregnancy had shown a normal appearing fetus with no abnormalities in head circumference or femur length and suggested normal fetal development. An autopsy disclosed fetal hydrocephalus and spirochetes were identified in fetal brain by indirect immunofluorescence (Fig. 5). Postpartum maternal blood showed a nonreactive result in Lyme serology.

Case 8: Fetal Lyme Borreliosis with Miscarriage at 16 Weeks Gestation

A 21-year-old black woman was admitted in July 1988 in active labor in week 16 of her third pregnancy. In the 2 weeks before admission, she experienced vaginal bleeding, abdominal cramps, low-grade fever, and on the day of admission noted a foul-smelling vaginal discharge. A 150-gm macerated male fetus showed no malformations at autopsy. Spirochetes were identified in fetal brain with immunohistochemistry using monoclonal antibodies (Fig. 6). Postpartum maternal blood was negative for antibodies to *B. burgdorferi*. No inflammation was found in fetal viscera at autopsy.

Case 9: Fetal Lyme Borreliosis with Miscarriage at 12 Weeks Gestation

A 25-year-old white woman was admitted in active labor in November 1986 at week 12 of her third pregnancy. She delivered a nonmacerated 294-gm male fetus in the emergency room. An autopsy disclosed no external or internal anomalies. The patient's two previous pregnancies had ended at 8 weeks and 26 weeks gestation; neither fetus had been examined histologically. Routine sections showed no inflammatory infiltrates. Culture of fetal viscera in BSK medium yielded *B. burgdorferi* and other bacteria from fetal kidney (Fig. 7), although no spirochetes were found in cultures of fetal brain, liver, spleen, heart, or thymus. No spirochetes were identified in fetal viscera using immunohistochemistry.

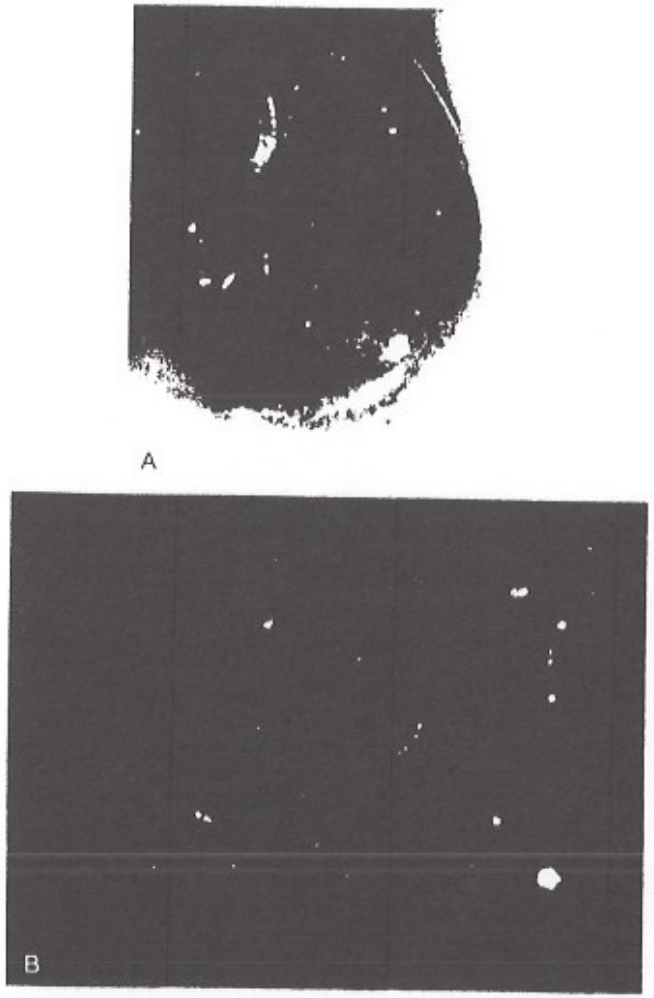

Figure 5. *A*, Fetal autopsy brain showing hydrocephalus. *B*, *B. burgdorferi*. Indirect immunofluorescence, 1500× original magnification, imprint cytology monolayer from autopsy brain.

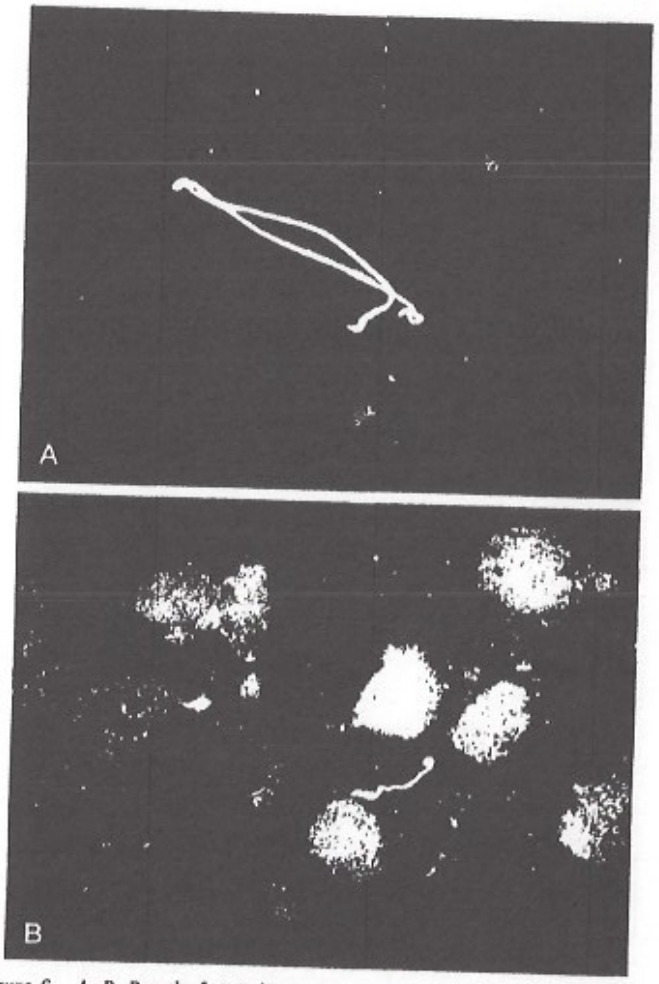

Figure 6. *A*, *B. Burgdorferi*, indirect immunofluorescence, autopsy brain imprint preparation, 1500× original magnification. *B*, *B. burgdorferi*, indirect immunofluorescence, autopsy brain imprint preparation, 1500× original magnification.

Case 10: Fetal Lyme Borreliosis with Intrauterine Death at 25 Weeks Gestation

A 27-year-old black woman was admitted for induction of labor at 25 weeks gestation after a routine obstetric ultrasound examination confirmed that the fetus had died in utero. No high-risk factors were noted in the patient's prenatal care record and no infections were identified. The

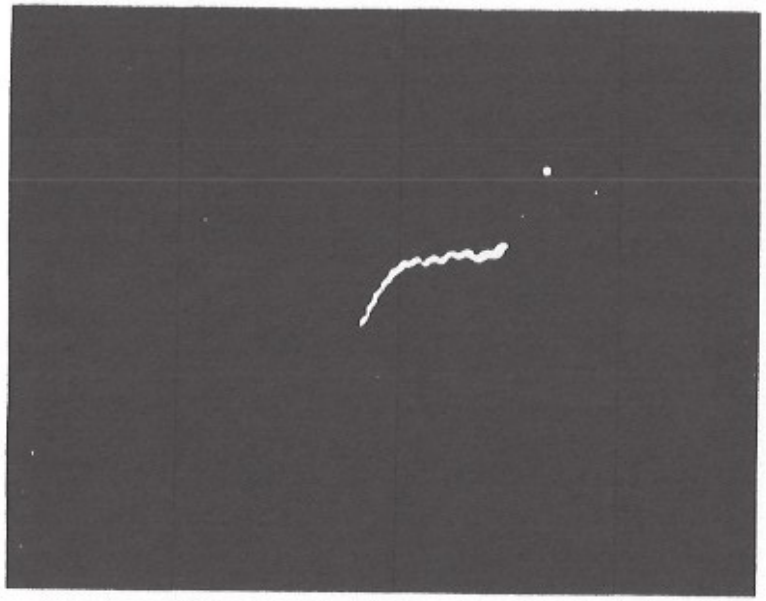

Figure 7. Borrelia species morphologically consistent with *B. burgdorferi*, darkfield microscope image 400× original magnification. Culture of autopsy fetal kidney in Barbour Stoenner Kelly medium.

patient reported in retrospect that she had experienced myalgias, arthralgias, and episode of headache for which she did not seek medical attention. A macerated male fetus showed no external anomalies at delivery. An autopsy showed a large intraventricular septal defect without additional internal anomalies. Postpartum Lyme serology performed on maternal blood was nonreactive. *B. burgdorferi* was identified in tissue by indirect immunofluorescence.

Case 11: Fetal Lyme Borreliosis Presenting as Neonatal Sepsis at Term Pregnancy

A 19-year-old black woman was admitted in January 1986 in active labor. She delivered an 8 lb 5 oz male infant who developed respiratory distress in the first hour of life and was transferred to a neonatal intensive care unit at a university hospital. Examination of the placenta revealed otherwise normal appearing villi which contained rare *B. burgdorferi* spirochetes (Fig. 8). The infant responded to intravenous antibiotic therapy.

Case 12: Fetal Borreliosis with Toxemia of Pregnancy and Neonatal Sepsis

A 26-year-old white woman was admitted in December 1985 at term pregnancy. Toxemia of pregnancy had its onset in week 37 of her

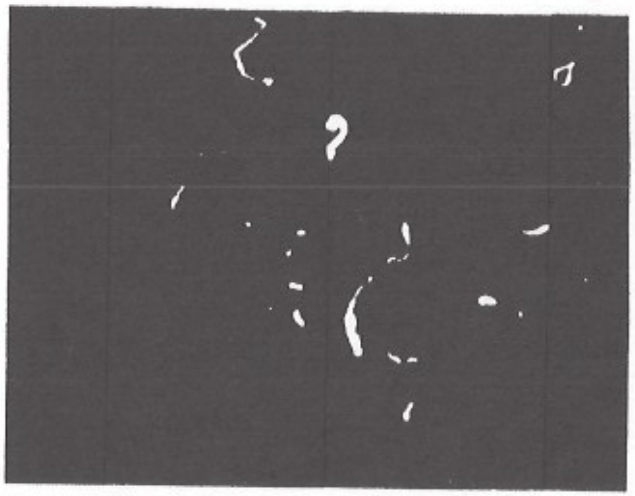

Figure 8. Various forms of Borrelia spirochetes including a small ring form, umbilical cord blood specimen, Indirect immunofluorescence, 1000× original magnification.

pregnancy and was manifested as hypertension and proteinuria. The infant weighed 4 lb 12 oz at delivery and appeared healthy and active in the delivery room. Respiratory distress ensued in the first day of life and was associated with hypoglycemia and fever. The infant was treated with intravenous penicillin and metronidazole for septicemia of unknown cause after routine bacteriology cultures yielded no pathogens. At the request of the attending pediatrician, the placenta was re-examined for spirochetes by Warthin starry silver impregnation. Many spirochetes were found in the placenta (Fig. 9). The infant is now 3 years old, and has shown normal growth and development. The mother has carried a second pregnancy to term and her second child is healthy.

Case 13: Maternal Lyme Borreliosis with Persistent Placental Spirochetosis Despite Oral Penicillin Therapy in Second Trimester

A 28-year-old white woman was admitted in November 1986 in active labor at term pregnancy. Lyme borreliosis had been diagnosed in her second trimester when erythema migrans was found on the skin of her back. She took 500 mg of oral penicillin VK for 15 days, and the erythema migrans lesion faded and disappeared in the eighth day of therapy. One month later she consulted a cardiologist because of complaints of dizziness. Sinus tachycardia was diagnosed by ambulatory cardiac monitoring. She delivered a healthy appearing 8 lb 13 oz male infant. Serology tests were negative for antibodies to *B. burgdorferi* in maternal blood and in umbilical cord blood from the infant by both IFA and ELISA methods. Culture of the placenta in BSK medium yielded motile spirochetes resembling borrelia species which could not be subcultured. Warthin starry silver impregnation yielded spirochetes in pla-

Figure 9. *B. burgdorferi*, various forms, placenta, 1000× original magnification, Warthin starry silver impregnation.

cental villi (Fig. 10). A retrospective interview disclosed that 2 weeks before delivery, the patient had sought medical attention because she noticed an Ixodid tick attached to her right leg. A 13 by 13 mm erythematous patch not consistent with erythema migrans was identified by her physician. Both mother and infant were retreated with oral penicillin plus probenecid after delivery. Neither patient developed a Herxheimer reaction. Mother and child appeared well in several follow-up visits.

Case 14: Maternal Lyme Borreliosis in Second Trimester of Pregnancy Followed by Toxemia of Pregnancy

A 23-year-old white woman was admitted to the hospital in her second trimester of pregnancy with concurrent erythema migrans and aseptic meningitis. Serology for Lyme disease was negative during the acute illness and remained negative in the convalescent period through term pregnancy. She was adequately treated with intravenous aqueous penicillin for 10 days. The erythema migrans lesion gradually disappeared by the third day of antibiotic therapy. The patient was closely monitored for the remainder of her pregnancy. In October 1986, 12 days before term, she was readmitted for mild toxemia of pregnancy presenting as hypertension which was treated with bedrest. She delivered a healthy male infant. Placental examination yielded no spirochetes by either culture or by histologic methods. Mother and child appeared well in serial follow-up postpartum visits.

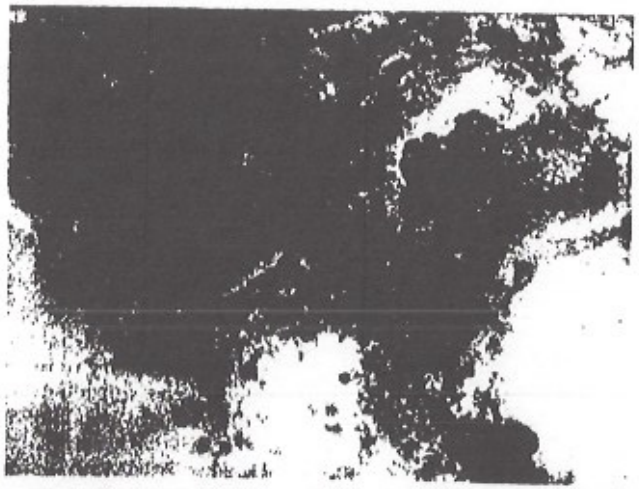

Figure 10. *B. burgdorferi* in placenta, 1500× original magnification, Warthin starry silver impregnation.

RATIONALE FOR A PROSPECTIVE STUDY OF SUDDEN INFANT DEATH SYNDROME (SIDS)

Clinical and pathologic study of fetuses and infants with fetal borreliosis acquired in utero indicate that the expectations do not always correspond with the observations in the cohort. Three observations which accrue from the cases of fetal borreliosis are:

1. Tissue inflammation is absent in fetuses with transplacentally acquired *B. burgdorferi* infection.
2. Gestational Lyme borreliosis may be associated with fetal death in utero, fetal death at term, or infant death after birth.
3. Maternal blood is seronegative for specific antibodies against *B. burgdorferi* in cases where the spirochete can be demonstrated in the fetus or placenta.

Syphilis acquired in utero could in some cases present with death of the infant in the first year of life.[8] Some of the infants with prenatal syphilis who died showed no clinical evidence of the infection when they were delivered. These observations from the clinical experience with syphilis led the author to test the following hypothesis. Some cases of sudden infant death syndrome (SIDS) might be circumstantially associated with subclinical persistent *B. burgdorferi* infections which were acquired in utero.

Permission to study 10 cases of SIDS was obtained from the Chief Medical Examiner of Suffolk County, New York. All cases were certified as SIDS[10] using the strict criteria of forensic pathology, all cases had been thoroughly examined with a detailed autopsy, routine histology, and toxicology studies. A condition of the study was that strict patient confidentiality be maintained. Sections of the heart, brain, kidney, and liver were prepared and Warthin starry silver impregnation was performed. Two of the ten cases showed spirochetes morphologically consistent with *B. burgdorferi* in the infant brain; one of the cases was a male infant who had died suddenly at 4 months of age (Fig. 11); and the second was a female infant death at 4 months of age. Spirochetes were not identified in the representative sections from kidney, liver, or heart. No inflammation was identified in the microscopic fields which contained the spirochetes.

SUMMARY

Great diversity of clinical expression of signs and symptoms of gestational Lyme borreliosis parallels the diversity of prenatal syphilis. It is documented that transplacental transmission of the spirochete from mother to fetus is possible. Further research is necessary to investigate possible teratogenic effects that might occur if the spirochete reaches the fetus during the period of organogenesis. Autopsy and clinical studies have associated gestational Lyme borreliosis with various medical problems including fetal death, hydrocephalus, cardiovascular anomalies, neonatal respiratory distress, hyperbilirubinemia, intrauterine growth retardation, cortical blindness, sudden infant death syndrome, and maternal toxemia of pregnancy. Whether any or all of these associations are coincidentally or causally related remains to be clarified by further investigation. It is my expectation that the spectrum of gestational Lyme borreliosis will expand into many of the clinical domains of prenatal syphilis.

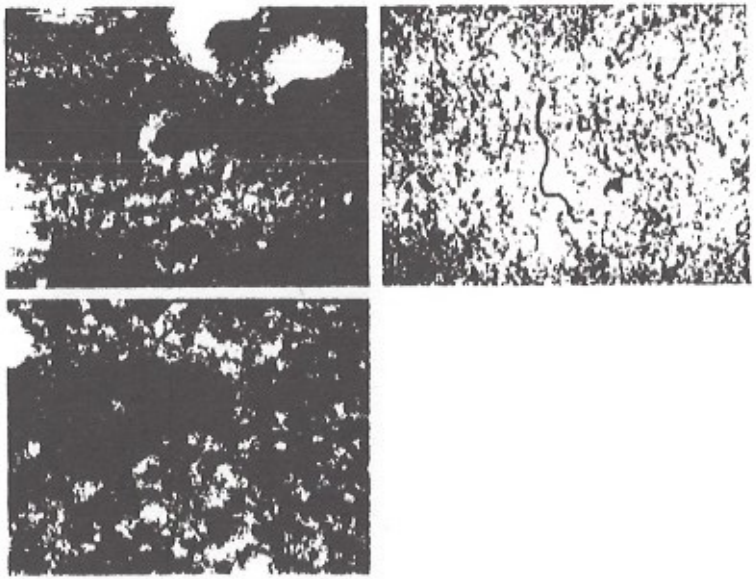

Figure 11. *A*, Borrelia species morphologically consistent with *B. burgdorferi*, 1750×, Warthin starry silver impregnation, autopsy brain, sudden infant death syndrome; infant age 4 months. *B*, *B. burgdorferi* reference strain B31, suspended in agar, Warthin starry silver stain, 1750× original magnification. *C*, Borrelia species morphologically consistent with *B. burgdorferi*, 1750×, Warthin starry silver impregnation, autopsy brain, sudden infant death syndrome; infant age 4 months. *D*, *B. burgdorferi* reference strain B31 suspended in agar, Warthin starry silver stain, 1750× original magnification.

ACKNOWLEDGMENTS

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Klinische Wochenschrift

Persistent Atrioventricular Block in Lyme Borreliosis

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Summary. Cardiac manifestations are reported in 0.3%–4.0% of European patients with *Borrelia burgdorferi* (B.b.) infection. Usually symptoms disappear within 6 weeks. We report a case with persistent impairment of atrioventricular (AV) conduction. Diagnosis was confirmed by demonstration of IgM antibodies and increase of IgG antibody titers against B.b. in serum, by isolation of the spirochete from skin biopsy material and by the typical clinical combination of erythema migrans, Bannwarth syndrome (meningoradiculitis), and complete heart block. Despite immediate antibiotic therapy with ceftriaxone, first degree AV block and second degree block Wenckebach with atrial pacing at 100 beats/minute persisted for 2 years. We conclude, that Lyme carditis can cause long-standing or irreversible AV conduction defects despite adequate and early antimicrobial therapy.

Key words: Lyme borreliosis – *Borrelia burgdorferi* spirochete – Lyme carditis – Atrioventricular block

Lyme borreliosis is the most common tick-borne disease in Europe and the United States [3]. In the Federal Republic of Germany about 1100 Borrelia infections were found in a seroepidemiological survey during 1984/1985 over a period of 19 months [22]. The causative agent *Borrelia burgdorferi* (*B.b.*) detected by Burgdorfer [4] is mainly transmitted by Ixodes ticks. Up to 30% of *Ixodes ricinus* ticks are infected in the Federal Republic of Germany [1, 36]. However only a low percentage (probably below 1%) of the persons bitten by ticks develop clinical symptoms of Lyme borreliosis [6, 17, 23].

Similar to syphilis, Lyme borreliosis is a multisystem disorder and may develop in three stages [1, 25, 27]. Typical clinical manifestations are erythema migrans (stage 1), lymphocytic meningoradiculitis Bannwarth, and Lyme carditis (stage 2), and acrodermatitis and arthritis (stage 3) [1, 8, 19, 25, 38]. Differences in the clinical symptoms between cases from Europe and the United States have been described. Such differences may be due to antigenic variations of Borrelia strains [34], but also may be caused by differences in the awareness of clinical symptoms [8]. In the United States cardiac manifestations were reported in 4%–10% [11, 26, 32], in Europe in 0.3%–4.0% of cases with Lyme borreliosis [2, 14, 21, 22, 24]. However, the latter observations were mainly based on seroepidemiological surveys.

Lyme carditis is characterized either by disease of the conduction system [20, 31] or by myopericarditis [12]. In the beginning usually second- or third-degree AV block is present. In the majority of patients conduction system abnormalities disappear within 6 weeks [13, 31].

We report on a patient with persistent pathologic AV conduction despite immediate and appropriate antibiotic therapy.

Abbreviations: AV = atrioventricular; AVt = atrioventricular time; *B. burgdorferi* = *Borrelia burgdorferi*; CSF = cerebrospinal fluid; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FRG = Federal Republic of Germany; I. damm./ricinus = *Ixodes dammini/ricinus*; IgG = immunoglobulin G; IgM = immunoglobulin M

Case Report

In September 1987, a 36-year-old woman was admitted to the intensive care unit of this hospital with chest pain, vertigo, nausea, vomiting, and severe bradycardia. The patient reported several tick bites acquired 8 weeks previously during a garden party. From the site of one of these bites in the middle of the lower abdomen an area of redness expanded reaching the size of two palms. On admission, the lesion had bright red outer borders with central clearing. Six days before she experienced pain in the lumbosacral area radiating into the buttocks and both legs.

The electrocardiogram on admission revealed sinus rhythm at a rate of 85 with complete heart block and junctional escape rhythm with a heart rate between 25 and 40 beats/min. Because of these severe symptoms, temporary pacemaker therapy was administered. Initially temperature was 37.5° C. The erythrocyte sedimentation rate (ESR) was 34 mm in the 1st h and the white-cell count was 14000. The first specimen of cerebrospinal fluid (CSF) showed 42 cells (75% lymphocytes) with albumin 31 mg/dl and IgG 7.5 mg/dl, suggesting a lymphocytic meningoradiculitis. Diagnosis of Lyme disease was confirmed by positive IgM antibody test and significant increase of IgG antibody titers against *B.b.* (immunfluorescence absorption assay as previously described [35], see Fig. 1) and by isolation of *B.b.* from the erythema migrans lesion by culture in modified Barbour-Stoenner-Kelley medium [15]. Borrelia specific antibodies were not detected within the CSF. Antibody tests for syphilis (Treponema pallidum hemagglutination assay and cardiolipin flocculation test), coxsackie- and hepatitisvirus were negative, as well as rheumatoid factor and antinuclear antibodies.

On assumption of Lyme disease with erythema chronicum migrans, neurologic and cardiac involvement, which was confirmed 6 days later by a positive borrelia IgM antibody test, an antibiotic regimen was started with 2 g ceftriaxone daily over 2 weeks.

The erythema faded within 6 days, body temperature and inflammatory signs in CSF and serum normalized, and back and leg pain subsided within days. However, symptomatic third-degree AV block was present for 5 days and second-degree AV block for 10 days. A prolonged PR interval of 220 ms (at a heart rate of 62 beats/min) and Wenckebach AV block at an atrial stimulation rate of 100 beats/min persisted until August 1989, 24 months after the initial hospital admission. Neither in exercise testing, nor in Holter monitoring for 24 h was second- or third-degree AV block detected at that time.

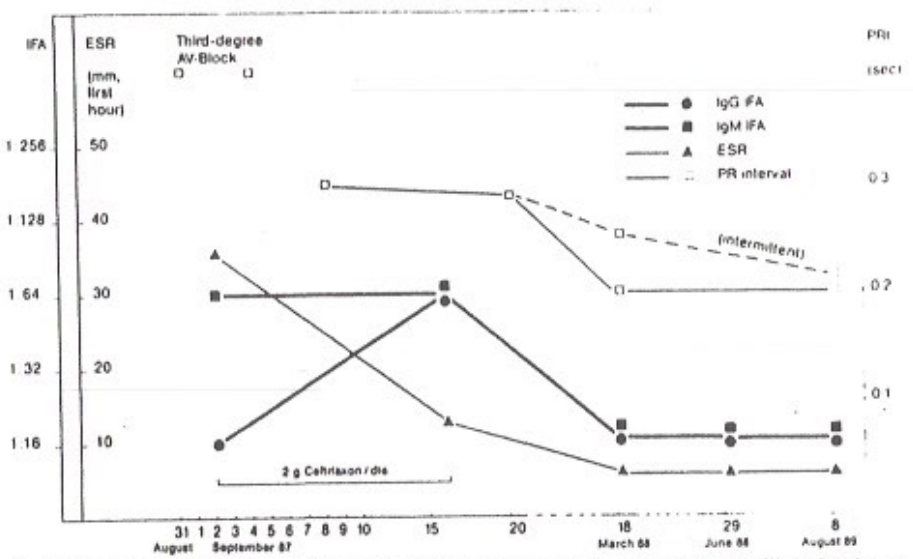

Fig. 1. The course of antibody titers against *Borrelia burgdorferi* (IgG and IgM immunfluorescence assay, IFA), of erythrocyte sedimentation rate (ESR), and atrioventricular block (PRI = PR interval in the electrocardiogram) in a patient with cardiac involvement in Lyme borreliosis

Discussion

Based on conclusive clinical observations AV block in Lyme disease has been reported as early as in 1977 before the spirochetal etiology was detected [31, 33]. Later on the borrelia as the etiologic agent was confirmed by microbial findings [7, 12, 13, 16, 20].

After typical features like tick-bite history, erythema migrans, and Bannwarth's syndrome our patient was admitted with third-degree AV block, insignificant IgG antibody titers and elevated IgM antibody titers. In the course of the disease a two-fold increase in IgG antibody titers and a gradual fall in IgM antibody titers was observed (see Fig. 1). With improvement of AV conduction antibody titers and humoral signs of inflammation declined. However first-degree AV block and Wenckebach AV block (at an atrial pacing rate of 100 beats/min) persisted for 2 years. Typical painless, asymmetric mono- or oligoarthritis did not appear.

The differential diagnosis must consider numerous diseases.

Rheumatic fever often simultaneously shows carditis, arthritis, and chorea. The carditis affects mainly the valves with changing murmurs, congestive heart failure, and accompanying pericarditis. Prolongation of the PR interval occurs in up to 50% of patients, complete heart block is unusual. The polyarthritis is acute and migratory involving the large joints of the extremities. The typical skin lesion erythema marginatum appears as a pink rash with central clearing in migratory fashion. Antistreptolysin titer may help in the differential diagnosis.

Sarcoidosis as a systemic disease affects multiple organs similar to Lyme borreliosis. Almost always the lungs are involved with symptoms referable to the respiratory system. Fibrosis can be detected in the chest X-ray as well as the typical hilar lymphadenopathy. Erythema nodosum is a sign of acute disease. Uveitis and unilateral facial paralysis are rare. Changing and transient arthralgias and frank arthritis are mostly limited to the large joints. Cardiac dysfunction is seen as well as arrhythmias and serious conduction disturbances with complete heart block.

Yersinia enterocolitica in young adults often resembles appendicitis, in elderly the typical enteritis with diarrhea and abdominal pain may be lacking. Erythema nodosum is seen in older women, 50% of patients have mono- (oligo-)arthritis (often HLA B 27 positive). The heart is involved as valvulitis and myopericarditis, conduction system abnormalities are rare. Serologic testing is helpful like in viral diseases.

The main "cardiotropic" virus is coxsackie B, which primarily affects the heart as myocarditis and heart failure with cardiomegaly. AV block is uncommon, as well as arthritis, skin involvement, or meningoencephalitis. Viral carditis often cannot be ruled out, because significant courses of antibody titers may be lacking.

Syphilis like Lyme borreliosis is caused by spirochetes and develops in stages. The primary chancre may be overlooked. The secondary syphilis is accompanied by sore throat, fever, malaise, weight loss, and headache. Lymphadenopathy is generalized, the skin shows small pale red macules, especially on the palms and soles. Alopecia areata and condylomata lata are other typical findings. Cardiovascular lesions are found in late stages. Medial necrosis of the large arteries with aortitis causes aortic regurgitation and aneurysm. Neurolues may be parenchymatous with general paresis and tabes dorsalis or meningovascular with stroke syndrome. The multiple serologic tests are very sensitive in making the correct diagnosis, but cross reactions may happen with *B.b.*

Reiter syndrome is characterized by the triad urethritis, conjunctivitis, and arthritis. The latter is acute, asymmetric, and oligoarticular. Mucocutaneous lesions and pleuropericarditis are rare. This disease is also HLA B 27 associated.

Most patients with lupus erythematodes develop painful nonerosive symmetric polyarthritis, which favors the small joints of the hands. The malar and discoid rash are photosensitive. Hematologic, and very variable neurologic disorders may be seen. Nephritis with persistent proteinuria accounts for most fatal cases. Pericardial pain accompanies the myopericarditis, the typical endocarditis Libman Sacks often is silent. Characteristic autoantibodies and the pathognomonic lupus cells support the diagnosis.

The so-called CREST syndrome in scleroderma lists calcanosis, Raynaud phenomenon, esophageal hypomotility, sclerodactyly, and teleangiectasia as the leading features. Cardiomyopathy with heart failure occurs as well as arrythmias with varying degrees of heart block.

Our case is readily recognized as Lyme borreliosis. Not only isolation of borrelia in typical skin lesions after several tick bites was present, but a conclusive course of IgG and IgM antibody titers confirmed the diagnosis. The concomitant development and later improvement of cardiac conduction defects in the absence of signs of one of the other diseases mentioned above makes an etiology other than borrelia highly unlikely.

Therapy usually consists of oral application of tetracyclines for early manifestation [29], in later stages of high-doses i.v. penicillin [28, 30, 31, 37]. Recent reports emphasize the susceptibility of *B.b.* to cephalosporins [9, 15] and clinical trials show their efficacy in patients [5, 18]. As suggested by serial antibody determinations our patient was successfully treated with ceftriaxone intravenously over 14 days. In parallel the erythema disappeared, inflammation signs in CSF and serum normalized, and AV conduction improved. However, the reason for incomplete restitution of AV conduction remains unclear. Persistence of borreliae is a possible explanation as well as scarring within the AV node.

If complete heart block persists for more than 1 day after initiation of antibiotic therapy, corticosteroids are recommended by some authors [31]. However, we did not treat our patient with corticosteroids because this regimen is discussed controversially [16] and may possibly reduce eradication of borreliae [5].

The prognosis of AV block in Lyme borreliosis is good. In an overview of 52 cases from the literature AV block resolved within 6 weeks in all but three [13]. No trial on the efficacy of antibiotic therapy in Lyme carditis is reported, but the administration of antimicrobial agents seems reasonable, because successful treatment has been shown in lymphocytic meningoradiculitis, the most common stage 2 manifestation [10, 18, 30]. Our case demonstrates that persistent conduction defects may develop despite immediate antibiotic therapy. As involvement of the heart is relatively rare in Lyme borreliosis, it is important to keep Lyme carditis in mind as potentially harmful.

Addendum

During preparation of this manuscript two similar cases, one with persistent disturbance of AV conduction have been published (De Koning J, Hoogkamp-Korstanje JAA, van der Linde MR, Crijns HJGM (1989) Demonstration of Spirochetes in Cardiac Biopsies of Patients with Lyme Disease. J Infect Dis 160:150–153

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Buchbesprechungen

P. Gerhardt, W. Frommhold: **Atlas of Anatomic Correlations in CT and MRI.** Anatomic Illustrations: K. Herzog. Translated by: H.N. Bertram. Georg Thieme, Stuttgart New York 1988. VIII, 173 pages, 329 illustrations, cloth DM 480,–

In dem vorliegenden Atlas wird die normale Anatomie von Kopf, Hals, Thorax und Abdomen in einer vergleichenden Darstellung von Zeichnungen, CT und MR-Bildern gezeigt. Die Qualität und Präzision der Zeichnungen ist brilliant. Die Zuordnung der CT und MR-Bilder ist gelungen und von guter Qualität. Die meist vorangestellten Topogramme mit der eingezeichneten Lage der Schicht ist sehr hilfreich. Durch die Auswahl nur einer MR-Sequenz, nämlich der Besten für die Anatomie in dem entsprechenden Fall, wurde insbesondere für den Nichtradiologen eine bestechende Übersichtlichkeit erreicht. Die Darstellung der verschiedenen Körperregionen in den 3 Ebenen, insbesondere in der sagittalen und frontalen Ebene ist durch die Kernspintomographie erforderlich geworden. Gerade durch die präzisen Darstellungen in den beiden letztgenannten Ebenen ist dieser Atlas besonders wertvoll. – Der vorliegende Atlas mit seiner hervorragenden Ausstattung ist sehr gut geeignet, die Anatomie in den modernen bildgebenden Verfahren CT und MR zu erlernen. Er ist aber ebenso ein nützliches Buch zum Nachschlagen für alle Ärzte, bei denen die CT und die KST eine wichtige Rolle für die Klinik spielt, insbesondere für Radiologen, Neurologen, Neurochirurgen und Chirurgen. Der relativ hohe Preis ist durch die sehr gute Ausstattung gerechtfertigt.

G. Fenzl (München)

H.H. Schild, F. Schweden (Hrsg.) **Computertomographie in der Urologie.** Georg Thieme, Stuttgart New York 1989. XVI, 332 S., 260 Abb. in 547 Einzeldarstellungen. Sb. Tab. Geb. DM 290,–

In dem vorliegenden Buch das von Radiologen und Urologen gemeinsam geschrieben wurde, liegt sicherlich eines der besten Computertomographiebücher vor. Die computertomographische Diagnostik in der Urologie wird umfassend und klinisch orientiert dargestellt. Kurze Kapitel über Technik und Kontrastmittel führen in die Methode ein. Das Kapitel CT-Anatomie ist für den Nichtradiologen sehr hilfreich. Es werden dann alle wichtigen Erkrankungen der Nebennieren und ableitenden Harnwege in der CT dargestellt. Am Beginn der Kapitel wird die klinische Symptomatik prägnant dargestellt. Aus ihr werden die Fragestellungen des Urologen an den Radiologen entwickelt. Die computertomographischen Befunde werden dann in guter Bildqualität dargestellt. Besondere Erwähnung verdient das Kapitel postoperative Computertomographie in dem neben allgemeinen postoperativen Komplikationen auch auf die Komplikationen und Änderungen der Organmorphologie nach speziellen Eingriffen, wie z.B. der ESWL und nach anderen Eingriffen an der Niere und am ableitenden Harnsystem eingegangen wird. Ein abschließendes Kapitel handelt in Grundzügen noch die Magnetresonanztomographie in der Urologischen Diagnostik ab. Das vorliegende Buch ist für Radiologen und Urologen unentbehrlich. Es ist ein wichtiges Nachschlagewerk für alle Kliniker, die urologische Diagnostik betreiben.

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Myositis caused by *Borrelia burgdorferi*: report of four cases*

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SUMMARY

Myositis was proven histopathologically in 4 patients (age range 36–66 years) who suffered from early or late stages of *Borrelia burgdorferi* infection. Muscle weakness was present in 3 patients, 1 complaining of additional myalgias. One man came to medical attention because of skin discoloration and swelling of one leg. Deep biopsy from skin, fascia and muscle revealed acrodermatitis chronica atrophicans, panniculitis, fasciitis, and myositis, respectively. Creatine kinase was slightly elevated in 3 cases and normal in one. Infiltrates were found in the perimysium and within the muscle bundles, mainly around small vessels. The infiltrates consisted of many B cells and T4 lymphocytes with fewer cytotoxic T cells, suggesting that *Borrelia* myositis might be due to a local immune response to unknown *Borrelia* antigens. Cultivation of *Borrelia* from muscle was not successful. Antibiotic therapy cured the myositis.

Key words: *Borrelia burgdorferi*; Myositis; Fasciitis; Muscular imaging; NMR

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INTRODUCTION

Lyme borreliosis is known to cause erythema migrans, facial palsy, meningoradiculopolyneuritis, lymphadenopathy, and occasionally hepatitis, splenomegaly, myocarditis and arthritis. Chronic or late manifestations include acrodermatitis chronica atrophicans, peripheral neuropathy and encephalitis in some patients. However, cases of myopathy due to Lyme borreliosis are rarely published. Schmutzhard and co-workers (1986) were the first to report a case of myositis in a woman suffering from erythema migrans and Borrelia-associated polyneuritis. Recently, Atlas et al. (1988) showed the presence of a few *Borrelia burgdorferi* by Dieterle silver stain in a further case of Lyme myositis.

We present here another 4 cases of interstitial and focal nodular myositis in early and late stages of *B. burgdorferi* infection. Investigation of these cases included biopsies for histopathological examination, skeletal muscle imaging and serological methods.

CASE REPORTS

Case 1

A 66-year-old previously healthy woman had sustained several tick bites over the past years before a bluish exanthema appeared on her left forearm. She had increasing difficulty in climbing stairs and walking quickly. She was admitted to our hospital in July 1986 about 4 months after the onset of muscle weakness. She complained about abnormal fatigue; however, muscular pain or sensory symptoms were absent.

Clinical examination showed a bluish-red skin lesion of 17 × 7 cm on the extensor surface of her left forearm. The skin in this area was partly atrophic, partly swollen and shiny. No regional lymphadenopathy or nodules were detectable. During neurological investigation muscle stretch reflexes could not be evoked. The right iliopsoas, left gluteus medius, and glutei maximi muscles, and the hamstrings on both sides, were markedly weakened. Trendelenburg's sign was positive on the left side. The patient had to use her arms to rise from a squatting position. No sensory disturbances were found. CK was normal on several occasions. The indirect immunofluorescence assay for *Borrelia burgdorferi* antibodies showed high titres in serum: IgG, 1 : 1024 (normal below 1 : 64); and IgM, 1 : 512 (normal below 1 : 32). IgM antibodies against a specific *B. burgdorferi* protein (pC) have been demonstrated by Western blotting (Fig. 1). The complement fixation test for FSME-IgM was unreactive, but positive for IgG. All other laboratory findings were normal. Cerebrospinal fluid analysis was normal, including serological testing for *B. burgdorferi* antibodies. The patient was positive for HLA-CW3. The motor nerve conduction velocity of the right peroneal nerve was normal; that of the left was reduced to 38 m/sec. H waves (m. soleus) were abnormal on both sides (52 msec, low amplitude), indicating a lesion of the S1 roots or of the proximal parts of the ischiatic or tibial nerves. An electromyogram revealed fibrillations and positive sharp waves in the right quadriceps femoris, the left extensor digitorum brevis and the tibialis anterior muscles on both sides. EMG of the left gluteus medius, biceps brachii muscles on both

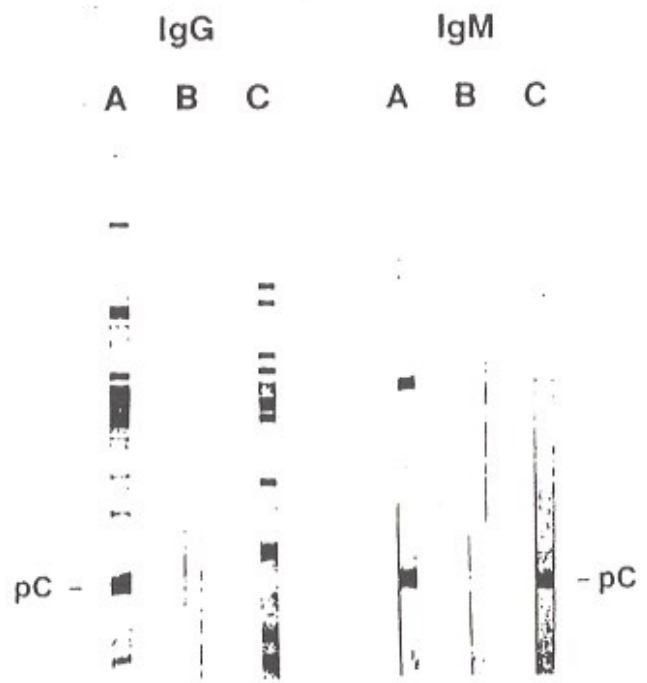

Fig. 1. IgG and IgM Western blots using *B. burgdorferi* strain PKo as antigen. A and B: positive and negative controls; C: serum from patient 1.

sides and the left abductor pollicis brevis muscle was normal, whereas in the extensor digitorum brevis muscles on both sides, polyphasic, high-amplitude units of long duration were seen. In the left gluteus maximus, right quadriceps femoris and the tibialis anterior muscles on both sides, potentials of short duration and low voltage, as well as motor units of increased amplitude and duration, were found.

Computed tomography of skeletal muscles was normal except for some hypodense foci in the paraspinals, whereas sonography of the rectus femoris muscles revealed slightly increased echointensities compared to the vastus intermedius muscles.

A muscle biopsy of the right rectus femoris muscle was performed. Perimysial connective tissue was focally enlarged. Numerous focal infiltrations containing histiocytes and lymphocytes were visible. They were localized in particular around small vessels (Fig. 2). In the vicinity of these infiltrations muscle fibres showed hyaline, granular and vacuolar fibre degenerations (Fig. 3). Necrosis of some fibres with phagocytosis was detected. Signs of fibre regeneration, such as fibre splitting and proliferation of satellite cells, were demonstrated. However, the great majority of muscle fibres was intact. Electron microscopy showed many lysosomes in histiocytes, indicating phagocytosis. Some muscle fibres showed autophagic vacuoles and, as a sign of exocytosis,

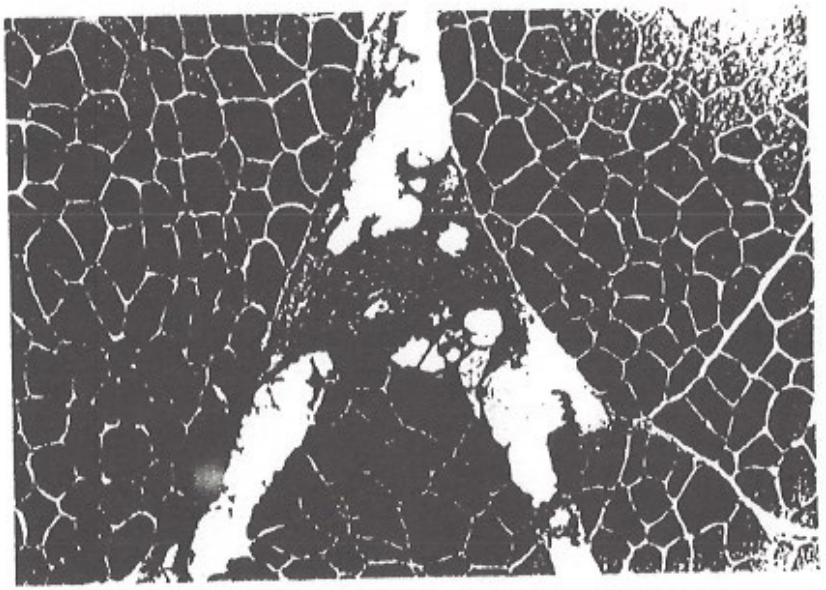

Fig. 2. Case 1: muscle biopsy specimen (right rectus femoris muscle) showing a perivascular lymphohistiocytic infiltration. Haematoxylin and eosin; original magnification, × 100.

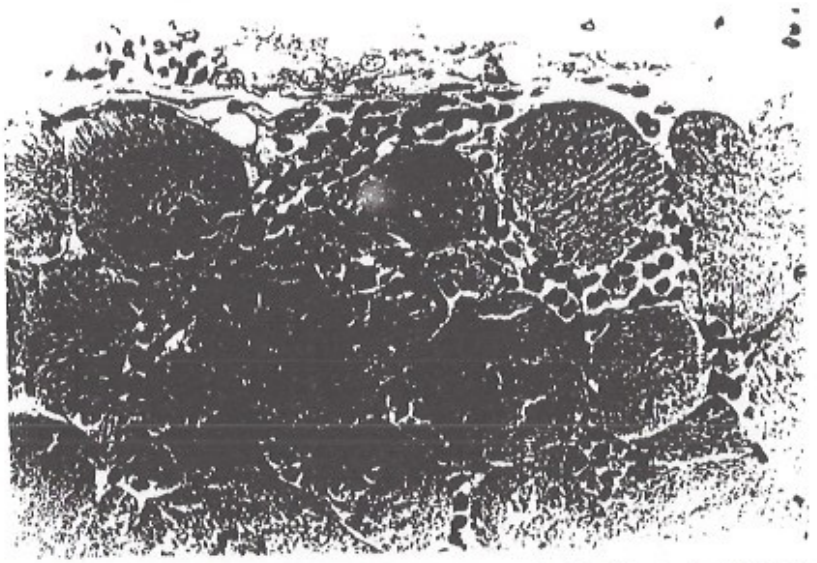

Fig. 3. Case 1: muscle biopsy specimen (right rectus femoris muscle). Small lymphohistiocytic infiltrate with fibre degeneration. Haematoxylin and eosin; original magnification, × 400.

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Histopathology of Clinical Phases of Human Lyme Disease

*Paul H. Duray, MD**

Lyme borreliosis (LB) in humans can be divided into acute, subacute, and chronic states of inflammation with variable degrees of dysfunction.[15,31-34] Multisystem involvement appears to be random and unpredictable, with chronic states of persistence in some cases. The disorder is one of inflammation, comprised of T and B lymphocytes mixed with macrophages, dendritic antigen-processing cells, and mast cells as the main components. *B. burgdorferi* has been demonstrated in virtually every tissue site recognized to be involved, with the exception of peripheral nerves and autonomic ganglia, although it is likely that the spirochete invades them as well.

Progress in defining the histopathologic changes in LB has been slow and pain-staking because patients are not readily biopsied as a routine practice. This is because signs and symptoms are generally transitory except for chronic, persistent involvement of the central and peripheral nervous systems, joints and synovia, and the skin. Sites sometimes involved by pain and swelling that are usually not biopsied include regional lymph nodes, gonads, and liver. Myocarditis is becoming increasingly recognized by clinicians who actively seek it, and transvenous right-sided cardiac biopsies have been performed more often in larger centers with a relatively high diagnostic yield. Tissue sites also proving satisfactory for biopsy purposes are the skin, underlying soft tissues, and voluntary muscle because of the complex differential diagnoses in these areas, including the differential of lupus erythematosus, scleroderma, fasciitis, Weber-Christian disease, dermatomyositis, rheumatoid nodules, gouty tophi, cutaneous malignant lymphoma, and polymyositis.

Many clinical cases are adequately treated with antimicrobials; other cases appear to undergo spontaneous "resolution," and still other patients—despite spirochete inoculation from the feeding tick—show no clinical signs of disease. That leaves the fourth group of patients who have demonstrated the variable clinicopathologic lesions that are discussed in this article. These changes will be discussed from the standpoint of acute, subacute, and late disease. In my experience, patients with documented LB serologically, who continue to have signs and symptoms referable to a given site or system, will have definite histopathologic changes in those sites upon biopsy, and in all likelihood will have demonstrable associated spirochetes, however sparse in number.

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CURRENT CONCEPTS OF SEQUENTIAL SYSTEMS INVOLVEMENT IN LYME DISEASE

The Beginning Lesion

The first manifestation of organ and tissue damage in the earliest phase of LD consists of the skin site where the nymph or adult female tick has fed. The tick-feeding site is a clinical hemorrhagic papule reflected histologically as a central ulcer underlayed by a mixed inflammatory infiltrate of polymorphonuclear leukocytes, macrophages, eosinophils, lymphoid cells, and scattered mast cells.[16] Some papules have areas of necrotic collagen with hemorrhage. The spirochete is deposited at the site, probably by accident from the tick during the blood meal, but is difficult to demonstrate histologically because of the profound polymorphous inflammation. Many spirochetes are doubtless phagocytized by neutrophils and macrophages, but others survive this first inflammatory response. The annular red rash may have central clearing, and this typifies erythema migrans (EM).[3,5,6,10,33] EM usually begins days after tick inoculation, persists in a range of 3 to 32 days, spontaneously resolves, or goes on to develop secondary, multiple ECM lesions.[3,32,35,37] Spirochetes have been isolated from the advancing red peripheries of the annular rash, as well as the secondary lesions. The spirochete can be histologically demonstrated by silver stains such as the Warthin-Starry,[10,12] Dieterle,[22] or Steiner stain.[12]

Acute Lyme Borreliosis (LB) Involvement

EM is reflected histopathologically by a mild to moderate infiltrate of lymphocytes and plasma cells, with few macrophages situated immediately around the small blood vessels of the papillary and upper reticular dermis.[10,17] Scattered mast cells also occur in this acute stage of LB, but are not in high numbers. The dermal vascular endothelium can appear swollen and prominent, with an occasional lymphocyte in endothelial cell cytoplasm, but luminal fibrin microthrombi, leukocytoclasia, and frank vascular necrosis have not been seen in EM. EM eventually resolves (with or without treatment), as the spirochete departs the skin and enters the general circulation (Fig. 1). Entry into the blood stream probably does not occur as an all or none critical event, but rather in a more or less random fashion while EM is still visible, because patients often complain of varied and protean symptoms referable to multiple organ systems, in a manner at once reminiscent of viral syndromes such as infectious mononucleosis. This can occur during the active rash, for example headaches,

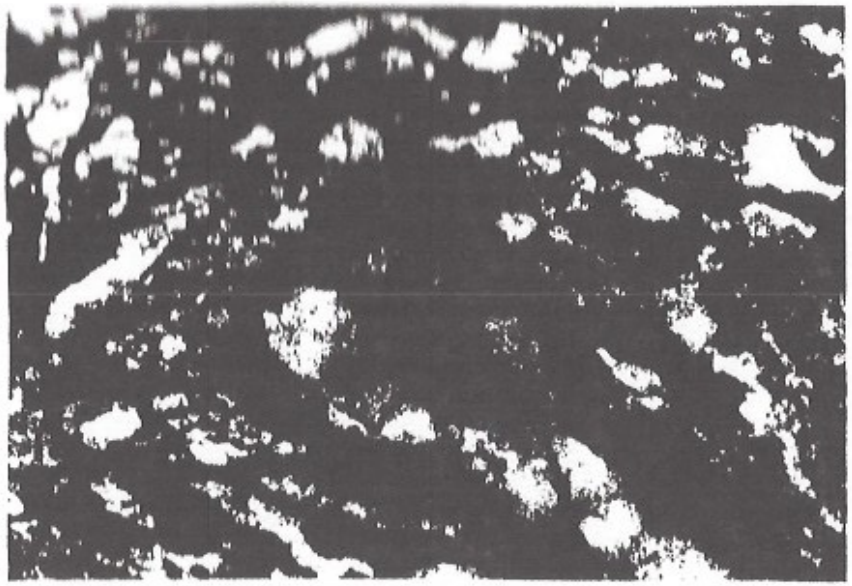

Figure 1. Erythema migrans. Spirochete has entered the dermal venule in the middle of the microphotograph. Dieterle stain, 1000×.

photophobia, nausea, and generalized aches may accompany the rash or follow it.[12–14,16] Clinical signs after the rash then include lymphadenopathy, mild splenomegaly, orchitis, fever, and conjunctivitis. All or none of these may be present in a given patient. Patients can complain of generalized flu-like myalgia, chills and headache, or alternatively symptoms of a nonspecific upper respiratory infection. The symptom that is prominent in the majority of cases, and is most likely to be the patients' major complaint is fatigue.[12] Chills and fever probably herald spirochetemia and humoral responses such as interferon release. The opportunity to examine the histopathology in lymph nodes, spleen, liver, lung, and gonads has been extremely limited because involvement of these organs in early disease is ordinarily benign and self-limited. Needle biopsies of the liver in three patients, one patient with lymph node biopsy, and two spleens from necropsy, however, have been studied by our laboratory. A plasma cell response in the lymph node paracortical regions and perivascular regions of the spleen were present. Swollen epitheliod sinus macrophages in the lymph node were abundant and showed erythrophagocytosis. Large, pleomorphic immunoblasts, were seen in both the lymph nodes and spleen (Fig. 2). These pleomorphic immunoblasts showed polyclonal IgG, IgM, κ and λ light chain immunohistologic reactivity consistent with the known serologic response of IgG and IgM in the serum. The immunoblasts did not react with Leu M-1 or antibodies to leucocyte common antigen, indicating that the lineage was plasmacytic. Plasma cell vasculitis as seen in syphilitic lymph nodes has not yet been

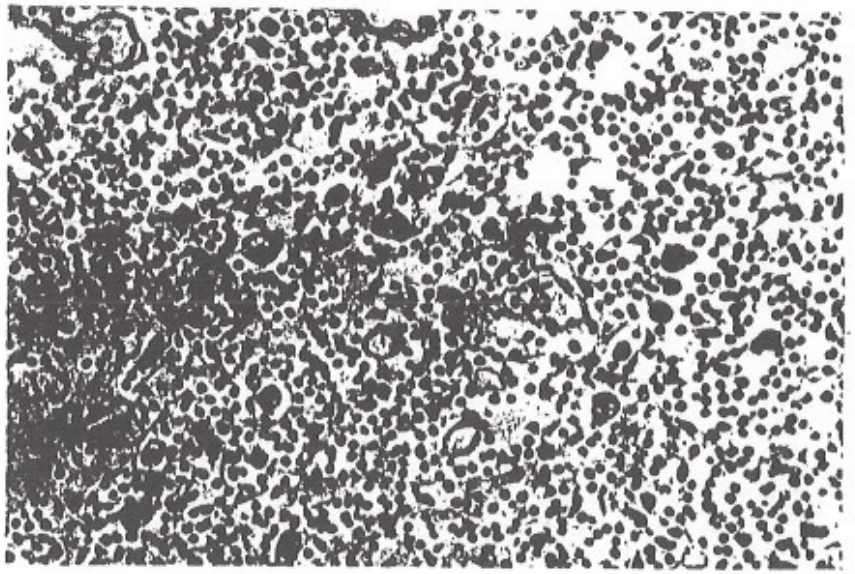

Figure 2. Lymphadenopathy during the flu-like stage. Note the atypical B-immunoblasts which are often seen in spleen and lymph nodes. Hematoxylin and eosin 400×.

seen in Lyme lymphadenitis. Nonspecific lymphoplasmacellular portal triaditis occurred in two patients, with intact hepatocytes, mild injury patterns of nuclear anisocytosis, and binucleate forms similar to changes seen in the livers of experimentally infected hamsters.[14] However, changes in a third case showed liver cell swelling and microvesicular fat changes reminiscent of acute viral hepatitis.[18] Many liver cell mitoses were also seen, in addition to diffuse mononuclear inflammatory cells (including plasma cells) throughout the sinusoids. The infiltrate focally suggested a neoplastic infiltrate when hypercellularity was mixed with liver cell mitoses. A rare triad vessel showed changes suggestive of mild vasculitis.

Interstitial pneumonitis has been seen in two patients in the Philadelphia area who were biopsied because of a suspicion for *Pneumocystis carinii* infection. A moderate lymphocytic interstitial infiltrate was seen in both as in viral pneumonitis but of lesser severity. Transient lymphocytic interstitial infiltrates probably correlates with episodic "dry" coughing encountered in some patients. Both patients had pleuritic pain, cough, and dyspnea and followed the onset of EM.

Human splenic infections have infiltrates of large, pleomorphic B and T immunoblasts in the follicular regions, or can rarely present with an acute splenitis requiring surgical intervention as occurred in one case. The latter had scattered areas of tissue necrosis, neutrophils, and macrophages accompanied by as many borrelial spirochetes as can ordinarily be seen in human Lyme infections. Splenomegaly and splenitis are probably indicative of dissemination.

Some patients manifest skin involvement in early disease by lesions other than EM. Urticarial lesions, cutaneous plaques, and malar, reddish macules have been seen but are not well-characterized at present. One case was confused with lupus profundus histologically because of deep dermal and subcuticular plasmacytic infiltrates in an angiocentric distribution, with abundant spirochetes in the intervening reticular dermal collagen. Cutaneous lymphoid hyperplasia (lymphadenosis benign cutis) does occur in the United States, although it is more commonly seen in Europe, and can arise in early disease.[3,4,8,36] It is manifested by erythematous swelling of the inferior or posterior ear, breast nipple, and axillary fold skin.[13] Other cutaneous sites are possible, but these are classic locations for borrelial lymphocytoma. Histologically, there are dermal lymphoid nodules with germinal centers and intervening dense fields of polymorphic lymphocytes including plasma cells and macrophages.[4,8,13] Spirochetes can be more easily identified in these lesions than EM by standard histologic silver stains and by electron microscopy. Borrelial lymphocytoma is probably under-recognized in the United States, although there could be strain differences accounting for its greater prevalence in Europe, especially Scandinavia.[37]

Symptoms of headaches, malaise, photophobia, nausea and vomiting, and pain in the musculoskeletal system especially the joints are perhaps more constitutional in nature than as a result of inflammation in those sites, but this is not fully known.

Progressive Dissemination

Two major systems comprise this phase: central nervous (15 per cent) and cardiovascular systems (8 per cent of cases).[16,30,33] There is some overlap of nervous system involvement between the acute phase (cephalgia; early meningeal signs), and disseminated nervous system involvement, which is characterized by the triad of meningitis, cranial neuritis, and radiculoneuritis.[24,25] Lyme meningoencephalitis seems to occur in European patients more often than in North American.[9] Multiple clinical combinations of head and neck polyradiculitis and encephalopathies occur in this phase, and may include Bell's palsy. Regardless of the neural structure involved (autonomic ganglia, longitudinal nerve, meninges, cerebral cortex) the basic histopathology involves a variable infiltrate of lymphocytes and plasma cells.[14-17] Linear infiltrates of lymphoplasma cells occur in the meninges and may correlate with the pleocytosis as seen in the cerebrospinal fluid. Cerebral cortical tissue, in my experience, has fewer lymphoid cells than peripheral neural structures, consisting mainly of increased microglial cells[15] and mild spongioform changes. Perivascular lymphoid cells have been seen in some cases. Meningovascular syphilis has more severe infiltrates and vascular changes than Lyme cerebritis, and gummas (cerebral necrobiosis) are absent in Lyme cerebritis as far as we know. Lymphocytes and lesser numbers of plasma cells are found directly within involved autonomic ganglia as they are in the peripheral nerves. Vessels within the longitudinal nerve segments can show vasculitis as well as abundant lymphocytes, macrophages, and plasma cells throughout the nerve interior and in the perineurium. It has not been demonstrated that *B. burgdorferi* occurs directly within ganglia and peripheral nerve segments as can be demonstrated in cerebral cortex, but this does not exclude the possibility that they are there.

Clinical involvement of the heart in disseminated disease is represented clinically by ventricular tachycardia or heart blocks (1°, 2°, complete).[23,28] Slow heart rates down to 30 per minute have been recorded. Although complete AV heart block often converts to normal sinus rhythm spontaneously, carditis has caused one death.[23] Lyme carditis pathologically is an epi- and transmyocarditis, with all regions of the myocardium involved by an interstitial infiltrate of lymphocytes and plasma cells.[17,23] Hyperacute involvement may involve small inflammatory nodules of neutrophils and macrophages as seen in a limited endocardial biopsy in one patient receiving chemotherapy for breast carcinoma, and in that case there was mild, focal myocardial sarcoplasmic degeneration which is ordinarily not seen in human Lyme myocarditis. Transvenous endomyocardial biopsy is effective in clinical diagnosis because the endocardial involvement is represented by a characteristic band-like infiltrate of lymphoid cells (Fig. 3). This band-like endocardial infiltrate has been seen so often that the diagnosis of Lyme carditis can be strongly suggested in an appropriate clinical setting (endemic areas with ECM history), even in limited endomyocardial biopsies. If the biopsy includes underlying myocardial fibers, the interstitial lymphoplasma-

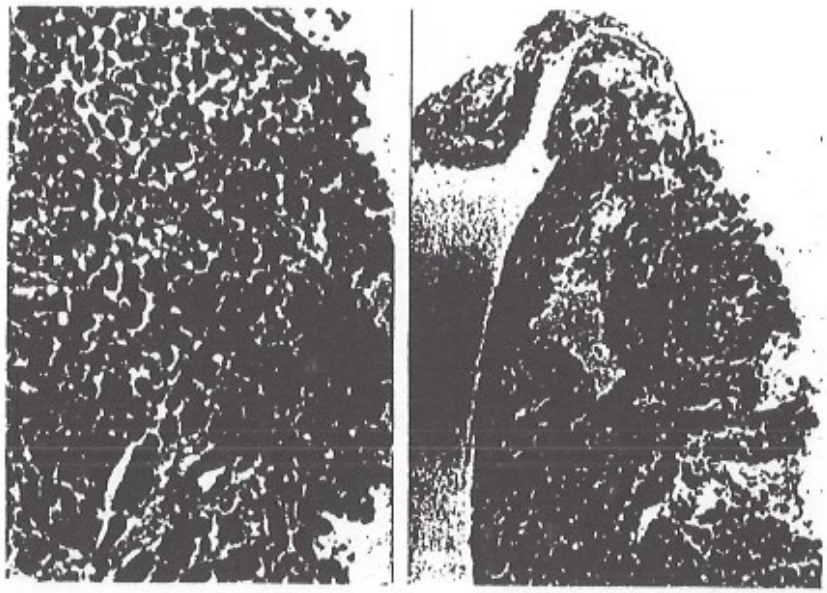

Figure 3. Lyme myocarditis. Interstitial lymphocytic and plasmacytic infiltration, *left*. Note the characteristic band-like endocardial inflammatory cell infiltrate of Lyme carditis. Hematoxylin and eosin.

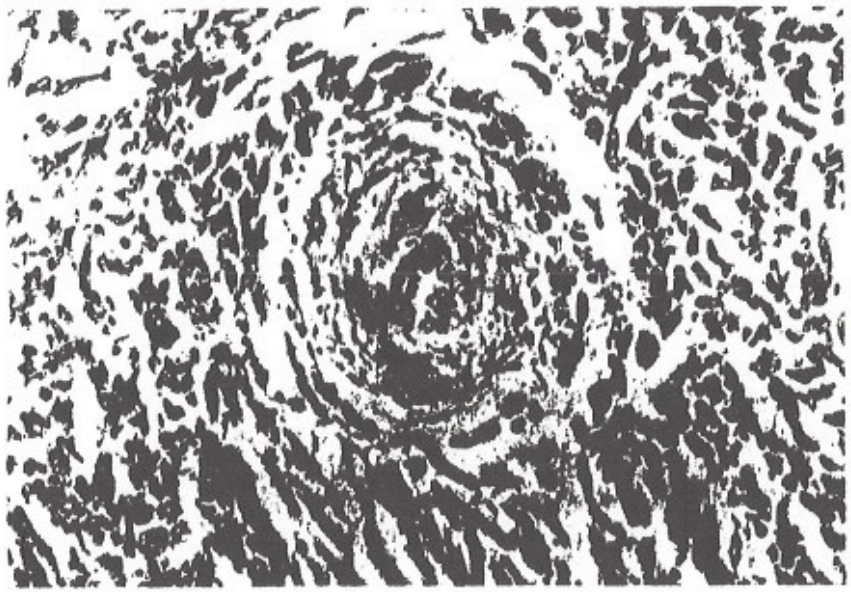

Figure 4. Lyme myocarditis. Hypercellularity of the adventitia reflecting a form of vasculopathy.

cytic infiltrate will be seen (see Fig. 4). Scattered small and large intramyocardial vessels show inflammatory changes that suggest a form of vasculitis. Occasionally, small vessels show endothelial cell swelling and a tight perivascular lymphoid response, while large vessels show adventitial infiltrates with loose reticulin and increased collager. formation (Fig. 4). Acute karyorrhectic neutrophilic vasculitis with fibrin microthrombi has not been encountered.

CHRONIC LYME BORRELIOSIS

A subset of patients go on to chronic, persistent disease in the presence of continuing spirochetes in selected sites with continuing inflammation and humoral immunologic reactions. These manifestations are not inevitable because the disease process may be completed at the end of each prior phase of the inflammatory illness, and not progress any further. However, chronic Lyme borrelial disease occurs worldwide predilecting for the skin and central and peripheral nervous systems in Europe,[6,9] and in the muscular skeletal system, particularly the joints and synovium, in North America.[29,33] This target organ selectivity in either hemisphere in chronic disease is a phenomenon not well understood but may relate to minor differences in the North American versus the European strains of *B. burgdorferi*.[39] The European strain has more flagella than North American strains. There are also minor differences in the outer surface membrane proteins. It could be speculated that varying

amounts of protein of a given molecular weight presented to the immune system at varying intervals could lead to unusual tissue responses with inappropriate target organ or structure damage. This concept needs to be explored experimentally with different *B. burgdorferi* strains in an appropriate animal model. These minor differences could play a role in target site specificity in chronic disease based on geography. The skin is also involved in late borreliosis,[2,8] and like the nervous system, chronic cutaneous involvement is perhaps more likely to be seen in Europe than in America.

Lyme arthritis and synovitis of the joints eventuates in approximately 60 per cent of Lyme disease patients in the New England area, and is ordinarily one of migratory and intermittent oligoarthritis.[29,31-33] In metropolitan Philadelphia there is no paucity of pediatric arthritis. The knee joint is the more likely site, but the shoulder, wrist, temporomandibular, and ankle joints are involved in some cases. I have not encountered histopathologic sections of the synovium in the earliest and hyperacute stages of involvement, but it is possible that neutrophils and macrophages occur in the synovial stroma, because many neutrophils are known to occur in the synovial fluid. The pathologic changes seen in the synovium will depend on the degree of involvement, the duration of involvement, and the extent of the sampling of the tissue (excision by subtotal synovectomy versus limited percutaneous biopsy). Limited samples may or may not show the key features of Lyme synovitis. The prevalent alteration is a nonspecific hypertrophic synovitis.[22] Hypertrophic synovitis can be seen in a variety of synovial disorders including post-traumatic synovitis, rheumatoid arthritis, and Reiter's disease. Lyme synovitis can be added to this list. The synovial membrane in this alteration is constructed of papillary fronds of synovial stroma lined by hyperplastic synovial cells of greater than the usual two-cell thick surface.[16,22] Hypercellularity varies from case to case. The hypercellularity is comprised of several cell types: synovial cells not only are in increased layers over the membrane but are found loosely distributed and infiltrating the subsynovial stroma. Varying degrees of lymphocytic infiltration are seen ranging from diffuse infiltrates up to lymphoid aggregates with poorly formed germinal centers. Lymphoid aggregates and follicles may be so prominent as to resemble lymph node or tonsillar architecture or to be sparse and focal. Plasma cells in various stages of maturation are seen in virtually every case, and may even be the predominant inflammatory cell responder in approximately 50 per cent of patients. Plasma cells are seen at the peripheries of the lymphoid aggregates, loosely distributed in small aggregates, or even found in the junctions of the synovial cell layer and the underlying stroma. The rest of the inflammatory cell infiltrate is comprised of mast cells and macrophages. Mast cells seem to be particularly prominent where lymphoid elements and plasma cells are fewer in number. Mast cells can be demonstrated in the vicinity of the deeper stromal vessels. Eosinophils have not been seen in Lyme synovitis. Neutrophils can be demonstrated on careful search, but are not a prominent finding in the phase of proliferative or hypertrophic synovitis.

Necrosis of either cells or stroma has not been seen in my cases, nor have alterations suggesting charcot joint formation been encountered.

However, up to 50 per cent of cases show deposits of fibrin and fibrinaceous material if the excision is adequate. Fibrin deposits are not specific for Lyme synovitis and can be seen in rheumatoid arthritis, Reiter's disease, and in hemophiliac hemarthroses. However, the fibrinaceous deposition in Lyme arthritis differs from the above by the presence of the fibrin matrix occurring diffusely within the subsynovial stroma of certain synovial villi. In the other conditions noted above, particularly Reiter's disease and rheumatoid synovitis, fibrin deposits are largely on the surfaces of synovial villi rather than extensively within the stroma of the synovium itself. This matrix deposition is not a form of (fibrinoid) necrosis, because the amorphic appearance of the stroma in fibrinoid necrosis and other forms of necrosis is not present in the fibrinaceous matrix of Lyme arthritis, and close examination shows fibrillar configuration. Intact mononuclear cells with patent nuclei are seen within the stroma indicating that this has not been stromal necrosis. In Reiter's disease and rheumatoid arthritis, the fibrin deposits for the most part tend to cover the synovial villous surfaces rather than replace the stroma.

It is known that vascular proliferation (neovascularization) accompanies most inflammatory tissue responses of any cause, with dilatation and congestion comprising the most common form of an acute flare and erythema. Granulation tissue represents a clear sample of microvascular proliferation occurring within a range of days to weeks. Microvascular proliferation consisting of branching (arborization), is seen in some patients with Lyme synovitis. This is nonspecific, and may relate to repeated episodes of localized trauma about the knee joint as a result of physical activity superimposed upon a background of tissue response to spirochetes. Many patients with Lyme arthritis have been of an age group where outdoor recreation and strenuous activity such as jogging has been commonplace. Again, based on tissue volume sampling, an additional change in the vessels can be demonstrated in up to one-third of Lyme arthritis cases. This is a form of obliteration of small arterioles within the stroma of the synovium, as a result of intimal cell proliferation (Fig. 5). Also accompanying this proliferation are varying degrees of collagenization. Both result in subtotal to total obliteration of the vascular lumens (see Fig. 5). Moderate vessel thickening also occurs in rheumatoid arthritis, but the obliterative vasculopathy as just described suggests Lyme arthritis. This would be especially true in synovial biopsies or excisions in an area that is endemic for Lyme disease. Clinically manifested synovitis has usually been present within a range of weeks to many months before biopsy or excision, and thus we do not know if there is active inflammatory vasculitis with fibrinoid and nuclear debris around and within these vessels at an earlier time. This microvascular obliteration possibly occurs at some point following a postulated more actively inflamed vessel, which would be demonstrated if the synovial tissue were sampled soon after the onset of synovitis. Even with limited excisions, we have seen these vascular changes upon careful examination. In some cases the cell proliferation is accompanied by an increase in adventitial cells yielding a vessel that has the (onion skin) appearance of vessels in the spleen of patients with lupus erythematosis. Even in a small, limited synovial sampling such as a transcutaneous biopsy, the combination of

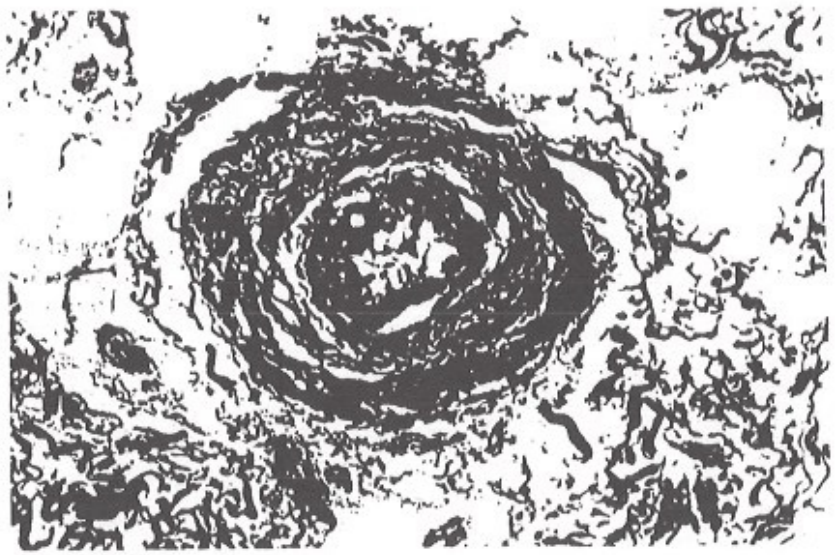

Figure 5. Endarteritis obliterans in Lyme synovitis. Trichrome stain 400×.

obliterative microangiopathy with fibrinaceous stromal deposition would be highly suggestive of the presence of Lyme arthritis. The majority of tissue samples will show deposits of hemosiderin scattered throughout, particularly in the deeper stroma. Mast cells are particularly prominent in areas of edema and in the deeper stromal regions, sometimes situated around vessels.

Spirochetes are seen in varying sites in the synovium in some cases. Despite careful search with appropriate silver stains, the organisms are not always demonstrated. Neither are they in great numbers as in other infectious microbial processes. They are found in the deeper collagen regions of the synovium, the immediate subsynovial layer of the stroma, and in areas of edema. Rarely one can find a spirochete in the vascular endothelium of the synovium or in a perivascular location (Fig. 6). No correlation with extent of disposition of the spirochetes is found with the lymphoplasmacellular infiltrate.

While none of the following features are diagnostic or specific for Lyme arthritis, if occlusive vessels are accompanied by prominent villous fibrin depositions (even up to 50 per cent of the tissue sampled), then Lyme arthritis should be considered. This is particularly true if the fibrinaceous deposition occurs in a subsynovial membrane and stromal location, in comparison with fibrin deposits occurring on the surfaces of the villin in Reiter's disease and rheumatoid arthritis. In limited synovial biopsy as well as in selected cases, fibrinaceous stroma may not be present and the lymphoplasmacytic villous hypertrophy may be the predominant change; lymphoplasmacytic villitis is the major histopathology in a good number of Lyme disease cases.

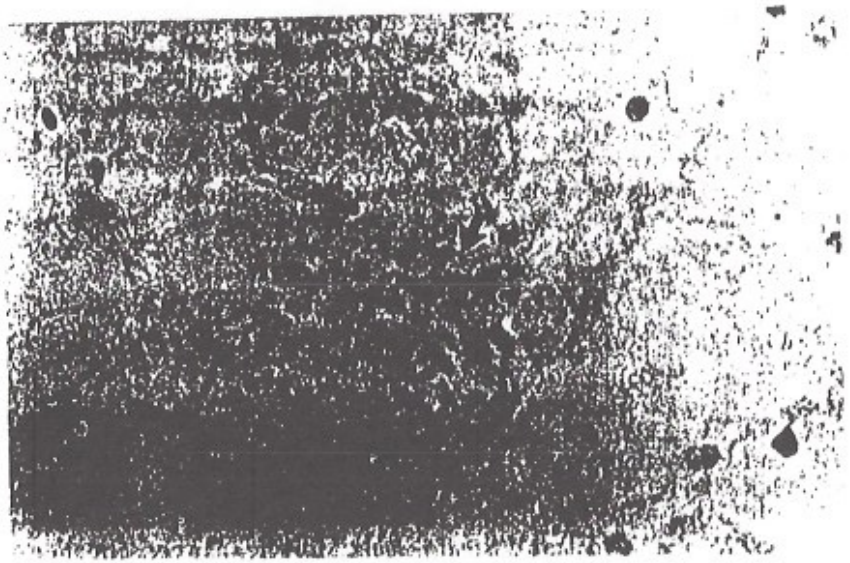

Figure 6. Lyme synovitis. Single spirochete in a pericapillary location. Dieterle stain 1000×.

CHRONIC CUTANEOUS INVOLVEMENT

The skin is involved in chronic disease as a consequence of the continuing presence of the spirochete in deep dermal and subcutaneous tissues. This may take place over a period ranging from many months to several years.

ACRODERMATITIS CHRONICA ATROPHICANS (ACA)

ACA is a peculiar, chronic, long-term Lyme dermatosis defined clinically as a purple, red-rubor discoloration of the skin, generally of the acral limbs, hands, wrists, forearms, elbows, or ankles and lower legs.[2,3,6,11,13] The peculiar rubor may be seen with a shining character to the skin surface. There is an early hypertrophic phase and a later atrophic phase wherein the underlying vessels are prominently displayed through the atrophic skin. ACA is more often seen in Europe than in the United States, generally occurring in the older patient. However, we have encountered this lesion in the United States. Rarely a peripheral neuropathy, that is, sural, ulnar, or radial, may coexist with the limbs involved by ACA, and again this occurs more commonly in Europe than in the United States.[20] Organisms have been cultured and demonstrated directly within the dermis of ACA.[2,15] The histopathology is nonspecific, but rather distinctive. The dermis is modestly thick with sheets of polymorphic inflammatory cells diffusely involving the entire dermis and infiltrating into the underlying hypocuticular fat in the hypertrophic phase of ACA, while the atrophic phase has hyperkeratosis and varying degrees of epidermal atrophy with loss or reduction of rete ridges. The dermis shows a characteristic dilatation of the dermal vasculature with widely dilated vascular lumens. Lymphocytes, plasma cells, macrophages, and mast cells are present in a mixture of the intervening dermal collagen (Fig. 7). Sporadic vessels will show occlusive vasculitis.

MORPHEA (LOCALIZED OR LINEAR SCLERODERMA)

The dermis in this condition resembles that of scleroderma (Fig. 8). An increase in collagen thickens the dermis beyond the level of the eccrine sweat glands, extending into the subcutaneous fat both in sheets as well as expansion of the fibroseptae which support the subcutaneous fat. Scattered collections of lymphocytes will be seen in the dermis of the morphea-like lesions and may be accompanied by collections of lymphoid cells in the subcutaneous fat. Plasma cells will also be present irregularly scattered around deep dermal vessels. Morphea as a consequence of chronic Lyme disease does not differ appreciably histologically from morphea due to other causes including the idiopathic form.

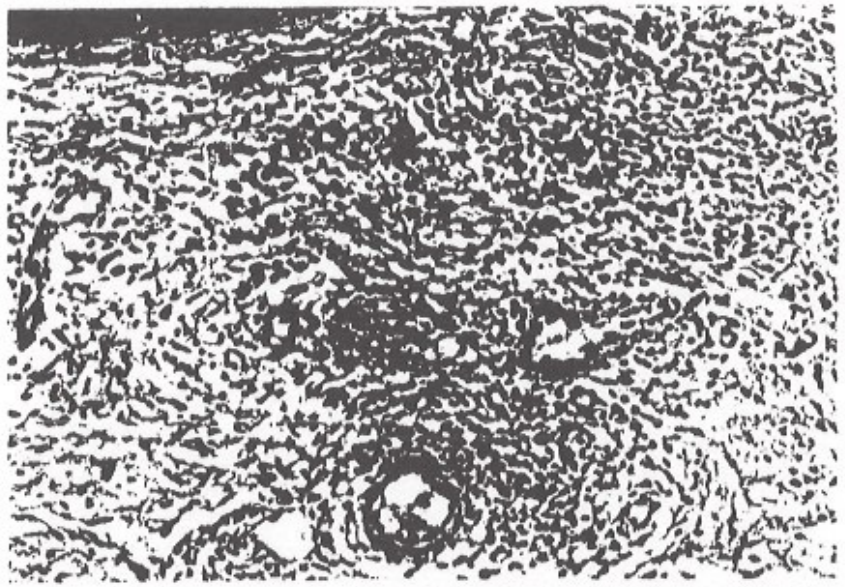

Figure 7. Acrodermatitis chronica atrophicans showing dermal inflammation. Many mast cells were seen in this example.

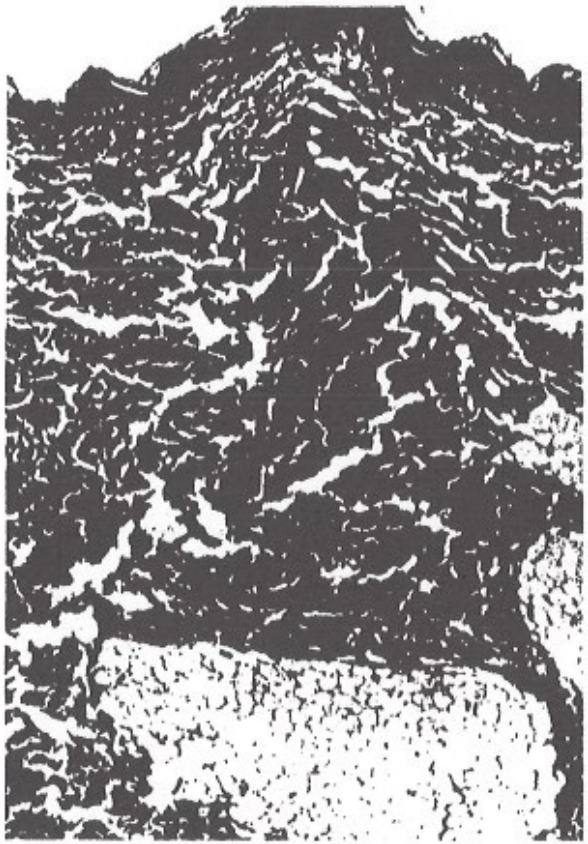

Figure 8. Lyme scleroderma (morpheaform). Hematoxylin and eosin 100×.

Eosinophilic Fasciitis

Two patients have been seen, one in Europe, where the clinical presentation of both patients was that of eosinophilic fasciitis. This involves a linear segment of skin with palpable thickness, with a tendency to be "hide-bound" as in linear morphea with some degree of pain and discomfort. Common locations are the lower extremities, and one case in the author's experience was on the forearm. The skin is drawn taut, with some erythema. Histologically, the epidermis was within normal limits while the dermis showed marked scleroderma-like thickening which extended into the subcutaneous fat, just as in morphea. Scattered aggregates of lymphoid cells and plasma cells distributed in a perivascular configuration with endothelial cell swelling and occlusion was seen in one case, which can also be seen in ACA (Figs. 9 and 10). Lymphocytes and plasma cells are found in the pannus. The fascia overlying the muscles is thickened, with edema, plasma cells, macrophages, and occasional eosinophils. Lymphocytes are found in a perivascular location, and scattered lymphocytic aggregates are seen in the interstitium of the subjacent skeletal muscle. There is probably some overlap between eosinophilic fasciitis and morphea, because the histologic features are nearly identical as regards the dermis and inflammatory response including plasma cells.

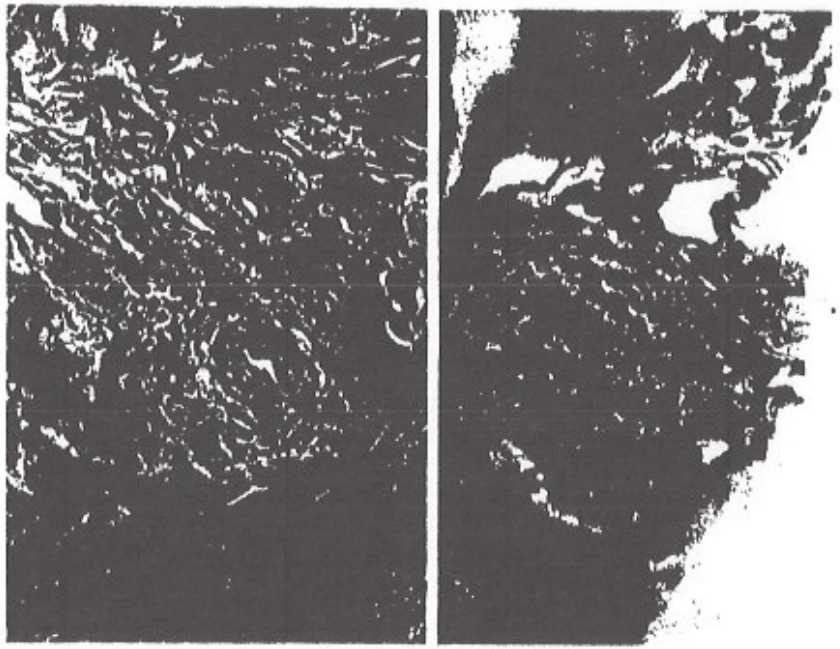

Figure 9. Changes of vasculopathy seen in chronic skin infection of acrodermatitis chronica atrophicans (ACA). Note the loss of the lumen *(right)*.

Lichen Sclerosis

Lichen sclerosis et atrophicus can now be added to the list of chronic cutaneous Lyme disease effects, although this is not a common manifestation.[1] Clinically these lesions look like lichen sclerosis in other clinical circumstances, and histologically the amorphic, edematous appearance of the collagen in the upper dermis is also similar. Lymphocytes and plasma cells are again seen in the deeper dermal regions below the area of edema and hyalinosis. Plasma cells are also found around thickened dermal capillaries and other small vessels. There may be more lymphoid cells and plasma cells in the perivascular location in Lyme cutaneous lichen sclerosis compared with other forms, but more experience with this interesting expression of Lyme disease is necessary to be certain.

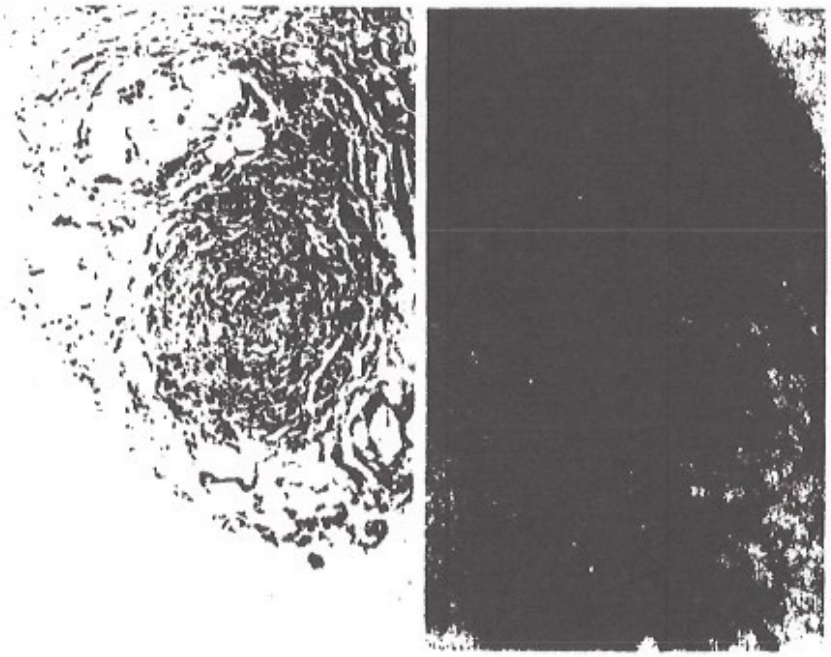

Figure 10. Left figure shows obliterated vessel in the subcutaneous fat. Spirochetes were seen in the upper dermis in this patient (right figure), and isolated in culture.

ULNAR FIBROUS NODULES

Ulnar fibrous nodules have not been seen in the United States Lyme cases to our knowledge, but seem to be more common in Europe, particularly West Germany and Scandinavia. These consist of subcutaneous firm fibrous nodules especially over the outer aspects of the elbows, and have a high association with concurrent acrodermatitis (ACA).[13,26] They may resemble rheumatoid nodules and tophi clinically, but differ somewhat in the texture of the fibrous nodules which are firmer. They may also occur near the elbow joints. Histologically they are composed of thick collagen bundles, with few fibroblasts in the intervening areas between the bundles. The vessels again show, in selected areas, mononuclear cells in a perivascular distribution, with vascular occlusion similar to those seen in Figure 8. Despite the implication of chronic scarring and collagenization, plasma cells still can be found.

LYMPHADENOSIS BENIGNA CUTIS (LABC)

LABC was discussed in the acute disease section and also mentioned here because the lesion may be one of duration beyond 6 months. LABC has been connected with Lyme disease in Europe for the past several

years, and is recognized to be a Lyme lesion in Europe. Its association with a tick bite history was also known historically in Europe. In Europe as stated previously, the classic location for Lyme LABC is the head and face, particularly the inferior ear lobes. Recently, involvement of the breast and axillary skin has been reported by Asbrink.[4] This is manifested by persistent, long-standing erythema and swelling. LABC is a form of cutaneous lymphoid hyperplasia, a lesion that has multiple etiologies including chronic antigen presentation. Spiegler-Fendt sarcoid, an old term, also fits the histologic changes seen in nonLyme LABC and Lyme LABC. The chronic form of Lyme LABC, like the acute-stage form, also consists of an intact overlying epidermis and a dermal expansion by proliferative lymphoid follicles with well-delineated germinal centers and varying thicknesses of the peripheral mantle zones. This can occupy an expanse of the entire dermis which yields the enlarged clinical lesion. The cells appear benign. In our experience, plasma cells have not been particularly plentiful but they can be found. This histologic pattern simulates the germinal centers as found in follicular hyperplasia of lymph nodes, tonsils, and even the appendix.

CONCEPT OF LYME DISEASE AS A VASCULOPATHY

None of the vascular changes seen in Lyme disease thus far have shown convincing evidence that this borreliosis is a form of classic, ongoing inflammatory vasculitis as the concept of vasculitis is ordinarily understood and described, as for example in Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss allergic vasculitis, and other forms of systemic vasculitis.[15,17] Neither have any changes resembled leukocytoclastic vasculitis, and anaphylactoid purpura. Changes of necrotizing vasculitis as seen in many other states are conspicuously absent. Also, the fulminant pathologic signs of syphilitic cutaneous vasculitis or vasculitis in syphilitic lymph nodes have not been seen in Lyme disease, but wider experience may prove this to be wrong. Despite this, there is strong evidence in certain tissue sites that a vasculopathy exists (see Figs. 5, 9 and 10), and that some histologic lines of evidence suggests that there had been more inflammation previously. Very little direct damage is seen in the dermal vasculature during acute EM, although there is a nonspecific endothelial cell swelling accompanied by an infiltrate that is immediately adjacent to the outer wall. The basement zone between the endothelial cells and the stromal matrix appears intact; however, because no red cell extravasation has been seen in any EM case in the author's experience.

VASCULOPATHY IN DISSEMINATED DISEASE

The microvasculature of the grey matter of the cerebral cortex nearest the leptomeningeal lymphocytic infiltrate have shown similar endothelial cell swelling with rare lymphocytes in the endothelium and vicinity. Myocardial vessels in Lyme carditis show more evidence of a form of

vasculopathy but not in limited right heart biopsies by transvenous catheterization. In one terminal case, the periadventitia was seen to show hypercellularity with beginning bands of collagen fibers in several medium sized vessels (see Fig. 4). The best evidence for vasculopathy comes from chronic, persistent lesions. A rather characteristic form, as stated previously, can be seen in from 20 to 30 per cent of long-standing Lyme arthritis cases with easily visible occluded vessels. Chronic cutaneous involvement including acrodermatitis chronica atrophicans, morphea, lichen sclerosis, and ulnar fibrous nodules, all show varying forms of vascular damage. Occluded vessels can be found in most of the above examples with the exception of Lichen sclerosis. In some ways the lesions of ACA show lymphocytic and fibrous vascular occlusion within the dermis, somewhat reminiscent of the lymphocytic vasculitis seen in Mucha-Habermann disease. However, red cell extravasation (especially at the dermal-epidermal zones and the epidermis as occurs in Mucha-Habermann disease) has not been seen.

Speculation on the Histopathogenesis

It is now clear that the presence of the spirochete directly within an organ site can elicit an immune and cellular response. Lyme borreliosis is an inflammatory state, and inflammatory cells correlate with the presence of *B. burgdorferi* or its products at the tissue site. Autoimmunity, however, can be postulated to be a factor in chronic disease. Spirochetes have now either been cultured or directly demonstrated by silver stains. The spirochetes are extracellular, and are often in the interstitial spaces or fibrous stroma of a given site. We have on rare occasion seen them within the endothelial cytoplasm or the perivascular regions, particularly in the synovium of arthritis patients.

There is phagocytosis occurring in the immediate period of inoculation in the skin by neutrophils, histiocytes, and possibly other cells. Those spirochetes that survive the initial phase of phagocytosis go on to establish infection and eventual dissemination, which seems not to occur in all patients. The cellular immune response within the tissue sites consists largely of prolymphocytes and adult lymphocytes and plasma cells. In skin and synovia, antigen-presenting dendritic cells, macrophages, and mast cells are also important participants. Directly within lymph nodes and the spleen, there is a brisk immunoblastic response, which thus far appears to be more accelerated than in other infectious diseases that we have experienced, due to the presence of collections of cytologically atypical immunoblasts. However, Epstein-Barr virus infections can also do this. This splenic and lymph node immunoblastic response can simulate early neoplasia, and correlates with B-cell stimulation and transformation. These transformed B cells appear atypical and at times pleomorphic, and we have demonstrated that they contain IgG and IgM and κ and λ light chains, but not IgA. This humoral and cell immune response could be a reaction to the surface antigens of the outer coat of the organisms. The antigens are comprised of at least 30 proteins which vary in their molecular weight. Common ones include 30, 31, 32, 34, and

41 kilodaltons. Barbour has shown that the proteins may be maximally expressed at certain times and under certain circumstances. These are variable major proteins which are expressed under different circumstances. As in relapsing fever (Tick-borne borreliosis, *B. hermsii*), the major variable proteins can fluctuate. Some of these surface antigens are immunogenic,and as they are recognized and processed as antigen, the immune system responds with specific antibodies. Antibody binding, followed by phagocytosis and intracellular killing of the spirochete may terminate the infection and lead to recovery. However, if a few organisms escape immunoreactivity by expressing genes that encode for different surface proteins, it is possible, and quite likely, that disease exacerbates because the immune system does not immediately recognize this new antigenic phenotype. There is evidence that the same mechanism of variable major protein phenotypic expression is occurring with *B. burgdorferi*, and if so, may account for reactivation of the spirochete after a seeming recovery months to years later, and which then leads to some of the chronic infections. Perhaps repeated expression of different genes with different phenotypes over a period of years leads to the seemingly unrelated and bizarre neural and cutaneous manifestations. This is quite different from the mechanisms of second and third stage syphilis, in that *T. pallidum* merely continues in the same target organ such as the brain, yielding a predictable histopathologic lesion. *B. burgdorferi* on the other hand, may have dormant and reactivation periods with subsequent immunologic secondary damage to organs and systems.

The Lyme spirochete has a predilection for central and peripheral neural tissues, especially in European patients. With continuing infection, demyelination is thought to occur in some humans. Demyelination may result from immunologic cross reactivity directed against variable major protein in a given infection. Regardless, demyelination does seem to be fundamental to many of the neurologic manifestations in chronic Lyme neural infections. At this stage the microvasculature in the vicinity of the peripheral nerves and within the nerve segment are damaged and associated with plasma cells. In the United States, chronic manifestations are most likely to induce arthritis and synovitis, rather than central and peripheral nervous system effects, although neural involvement does occur in the United States. It remains to be seen whether these tissue site prevalence differences are spirochete related or not.

Additionally, it is possible that some component(s) of organ and systems damage occurs because of the vasculopathy on an immune basis. Although spirochetes can be found in the endothelium and probably directly damage vessels themselves, the late stages of vascular damage could be a result of some form of continuing immune complex adherence. Eventual occlusion of the vessels then occur. Why this endarteritis obliterans is not seen in all patients, however, is not known. Perhaps given differences in B-cell allohaplotypes from case to case, there might be a difference in immune-complex production and circulation. Regardless of which pathway is operative and is responsible for the clinical pathologic syndromes, we believe the persistence and possible reactivation of *B. burgdorferi* over time is responsible for the immunologic response which then leads to organ and systems damage. The continuing

development of animal model systems for study of this important borreliosis will be major steps in answering the many unknowns.

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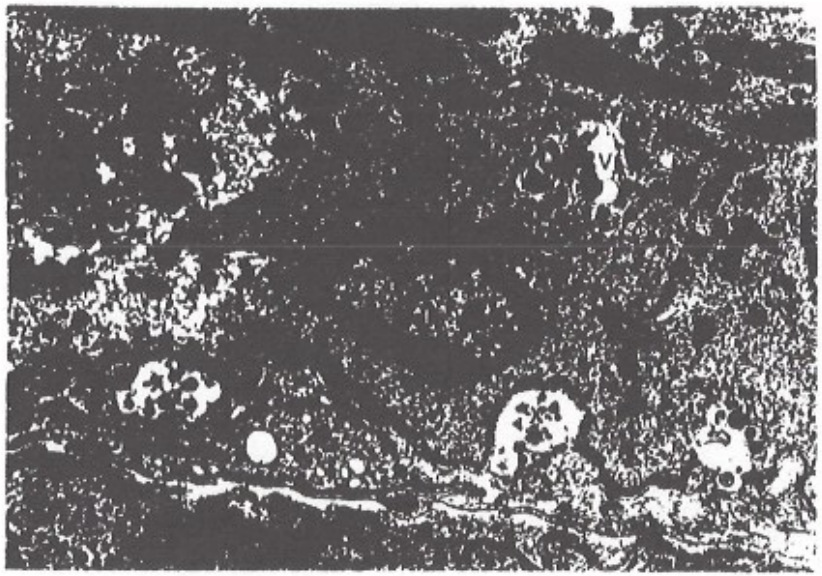

Fig. 4. Case 1: muscle biopsy specimen (right rectus femoris muscle, electron microscopy). In the subsarcolemmal region of a muscle fibre, a nucleus and autophagic vacuoles (v) are present. Directly beneath the surface of the muscle fibre in the intercellular space are extracellular electron-dense lysosomes (matrix granules) (x). Original magnification, × 14000.

spherical microparticles in the neighbourhood of inflammatory infiltrations (Fig. 4). Immunohistological staining indicated that most lymphocytes were B cells and T4 helper cells. Only a few cytotoxic T8 cells were visible. Many lymphocytes expressed DR-antigens, while some expressed interleukin-2 receptors. Cultivation of *Borrelia* from the muscle and attempts to visualize *Borrelia* by silver staining (de Koning et al. 1986) and immunohistological staining were not successful. Polyclonal rabbit antibodies against *B. burgdorferi* were used as primary antibodies. These antibodies were immunoenzymatically labelled using immune complexes of alkaline phosphatase and monoclonal anti-alkaline phosphatase (APAAP) complexes. Skin biopsy showed typical features of acrodermatitis chronica atrophicans, with atrophic epidermis, effacement of the rete ridges, diffuse dermal infiltration of mononuclear cells, particularly lymphocytes, fewer histiocytes and plasma cells in the upper and middle layer of the corium, oedema in the corium, and loss of elastic fibres in the upper corium.

Before admission to our hospital, the patient received 2 megaunits of penicillin per day parenterally over 4 days. She was treated with intravenous penicillin G, 20 MU/day for 10 days. As improvement was not satisfactory 8 weeks after therapy, we additionally administered 200 mg minocycline for 10 days followed by 100 mg minocycline per os for 2 weeks.

After completion of the therapy, a second biopsy was taken from the right rectus

femoris. Compared to the first biopsy, infiltrates were now less numerous; only few basophilic fibres with internal nuclei and granular changes were seen. Follow-up examinations were done repeatedly over an 8-month period. Muscle weakness slowly improved; the last investigation showed normal neurological findings. All tendon reflexes were brisk. Acrodermatitis chronica atrophicans disappeared, except for some teleangiectasia and apparent skin atrophy. H waves (m. soleus) had shorter latencies (40 msec on both sides) than before. On EMG, no myopathic pattern and spontaneous activity were detectable at this time. Antibody titres declined significantly (IgG 1 : 256, IgM 1 : 128).

Case 2

A 61-year-old man noticed swelling and redness with hyperthermia in the malleolar region of his right leg. In the course of 1 year, the exanthema extended and finally covered the whole leg. He reported tenderness in the leg and hypersensitivity to pressure. There was also slight pain in the lower back, but without spreading to the legs. The patient could not recall a tick bite. In his youth he had suffered from hay fever and later from bronchial asthma. Over the last 10 years there had been no signs of allergic diathesis, except swollen eyes during hay harvest.

Clinical investigation revealed swelling of the whole right leg with a brown-bluish discoloration, particularly on the extensor surface. All neurological findings were normal.

Venous thrombosis was ruled out by phlebography before admission to our hospital. Motor nerve conduction velocities of peroneal nerves and the sensory nerve conduction velocity of the left sural nerve were normal. On the right side, no nerve action potential of the sural nerve could be evoked. EMG showed normal findings in the right quadriceps and tibialis anterior muscles. In the medial head of the right gastrocnemius muscle, positive sharp waves were visible, while action potentials and interference patterns were normal. A complete blood count showed a slight increase in eosinophilic granulocytes, to 5 and 8% (normal range 1–4%). The erythrocyte sedimentation rate was 4 mm/h. IgE content was 1.80 g/l (normal below 1.00 g/l), and IgG 14.22 g/l (normal range 7.80–15.30 g/l). IgA and IgM levels were also normal. CK varied between 47 and 201 U/l (normal range 10–80 U/l). The amount of immune complexes measured by using the C1q-binding technique was elevated to 24% (normal below 10%).

Indirect immunofluorescence assay detected IgG antibodies to *B. burgdorferi* in a concentration of 1 : 4096 (normal below 1 : 64). The IgM titre was non-reactive. The cerebrospinal fluid/serum IgG index was normal. Protein content in the CSF was elevated to 0.79 g/l (normal range below 0.5 g/l). The *Treponema pallidum* haemagglutination test was non-reactive. The patient was HLA-CW3 positive.

Magnetic resonance imaging of the lower legs showed high signal intensities in the medial head of the right gastrocnemius muscle, almost exclusively in T2 weighted images (Figs. 5 and 6). These findings indicate an increase in intramuscular fat combined with oedema in the right gastrocnemius muscle (Schalke et al. 1987). An en bloc biopsy was taken from the medial head of the right gastrocnemius muscle and the adjacent fascia and skin. Infiltrates consisting of lymphocytes, lymphoid cells, histiocytes and

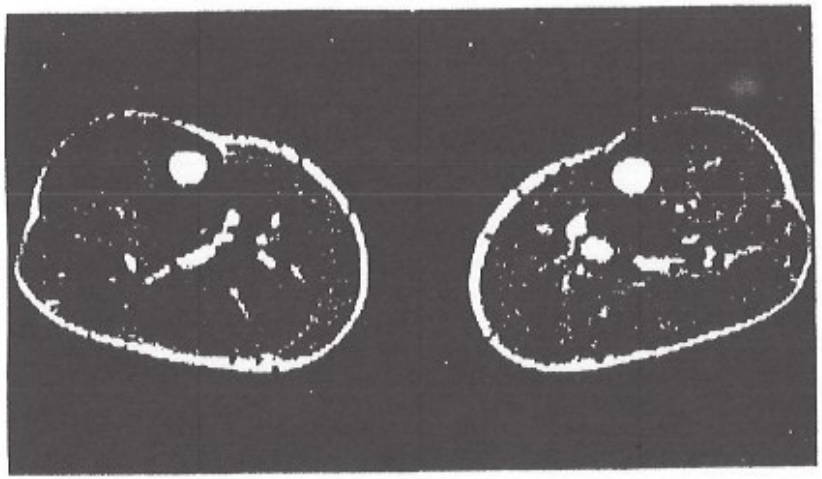

Fig. 5. Case 2: MRI of the lower legs (TR 1600 msec/TE 30 msec; before therapy). Only slightly increased signal intensities in the medial head of the right gastrocnemius muscle (left side of the figure).

plasma cells were present in subcutaneous layers, in fascia and in the muscle. There were no eosinophilic granulocytes. We found infiltrates localized predominantly in the perimysium near the fascia, but also in deeper layers of the muscle tissue. Most of the endomysial infiltrates were situated around small vessels, spreading into the neighbouring tissues. Fibre degeneration was seen close to the infiltrates. About 5% of all

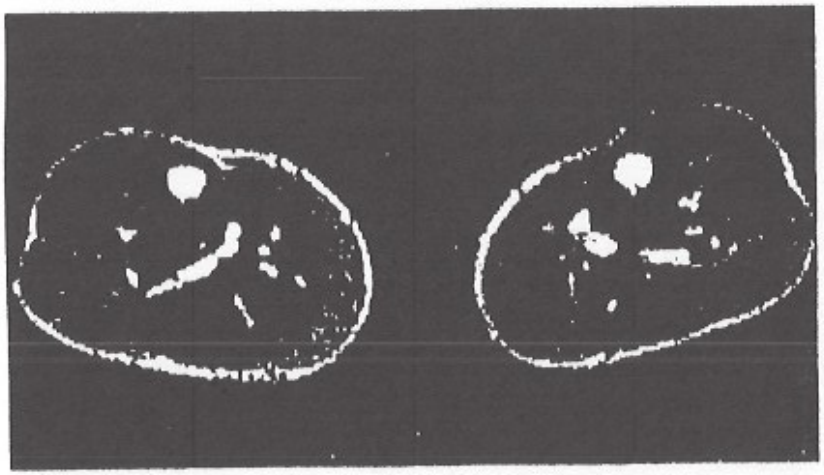

Fig. 6. Case 2: MRI of the lower legs (TR 1600 msec/TE 120 msec; before therapy). Markedly increased signal intensities in the medial head of the right gastrocnemius muscle (left side of the figure).

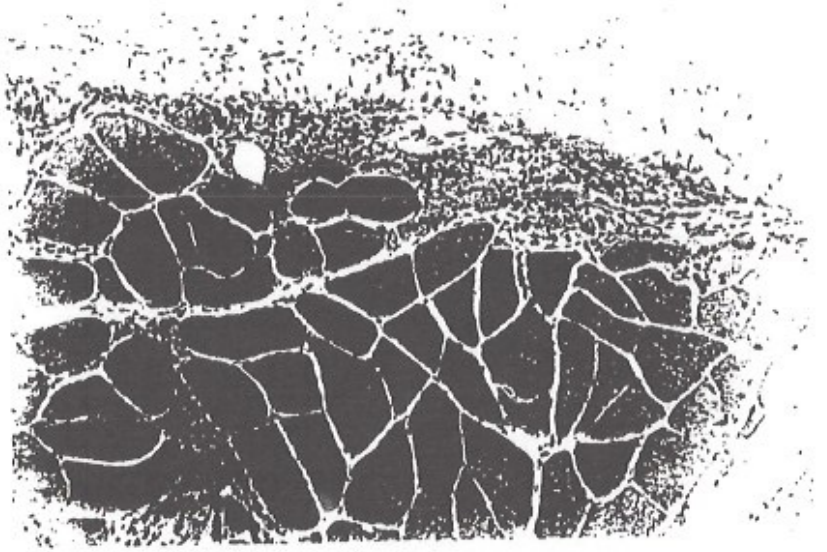

Fig. 7. Case 2: muscle and fascia biopsy specimen (medial head of the right gastrocnemius muscle). Lymphohistiocytic infiltration of the fascia and the muscle with beginning degeneration of muscle fibres and some fibre splitting. Haematoxylin and eosin; original magnification, × 100.

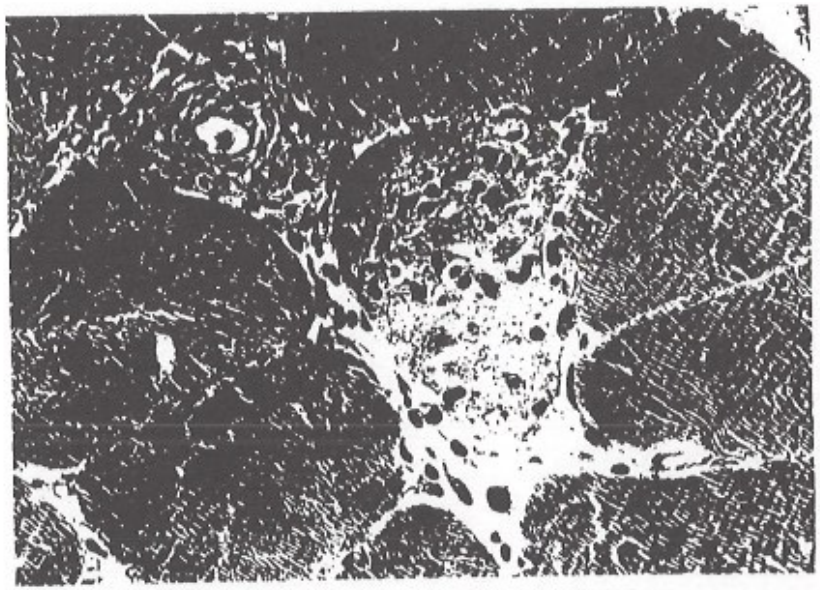

Fig. 8. Case 2: muscle biopsy specimen (medial head of the right gastrocnemius muscle). Small perivascular lymphohistiocytic infiltration and fibre necrosis. Haematoxylin and eosin; original magnification, × 400.

fibres were necrotic; the remaining muscle fibres were normal. Immunohistological findings were identical to those in case 1. The infiltrates consisted of many B lymphocytes and T4 helper cells, many of them expressing HLA-DR antigens and a few interleukin-2 receptors. Only a small number of cytotoxic T8 lymphocytes were visible in the endomysium. None of them invaded muscle fibres. Electron microscopy of the inflammatory fields showed the presence of activated histiocytes, often resembling epitheloid cells. Features of activated macrophages included abundant cytoplasmic processes, numerous mitochondria and electron-dense lysosomes. Attempts to isolate *Borrelia* from muscle tissue were unsuccessful. Staining methods, as described in case 1, failed to demonstrate *Borrelia* in muscle tissue.

Histopathological examination showed a thinned epidermis with obliterated rete ridges. There were perivascular infiltrates, consisting of lymphocytes, histiocytes and a few plasma cells, particularly in the upper corium, but also in deeper layers. Elastic fibres in the upper corium were rarefied. *B. burgdorferi* could be isolated from skin culture in a modified Kelly medium (MK-B-medium). The patient was treated with 3 × 2 g Cefotaxim for 5 days and then with 2 × 2 g Ceftriaxon for 9 days. Discoloration and swelling of the skin vanished almost completely within 3 months. IgG antibody titre against *B. burgdorferi* declined to 1 : 2048. MRI revealed lower signal intensities in the medial head of the right gastrocnemius muscle than in the first examination.

Case 3

This patient was a 36-year-old man. After a picnic outing he developed erythema migrans. The rash lasted about 14 days. He then developed fever, chills, tiredness, headache and myalgia, which were accompanied by profound muscle weakening. He complained about not having been able to get out of bed in the morning. Because of the flu-like symptoms, he finally consulted a physician, who diagnosed Lyme borreliosis.

On physical examination the right thigh muscle was swollen, tense, and painful. Serological examination by immunofluorescence showed reactivity for Lyme spirochaetal IgG antibody at 1 : 516. CK was 410 U/l (normal range 37–289 U/l). A deep muscle biopsy of the right thigh was performed showing the following pathologic changes: skeletal muscle fibres were largely intact. Abnormalities were confined to the regions of the small veins where lymphoplasmocellular infiltrates were seen clustered around vessels both inside and outside of the muscle fibre groups.

Following a 21-day course of oral penicillin, only 1 g/day in divided doses, the patient's myalgia and weakness improved clinically and he was able to return to work. However, his serum titre of 1 : 516 remained positive at the last test.

Case 4

A 37-year-old man gave a history of a tick bite in summer of 1987, which was not followed by a rash, but was accompanied by nausea and a headache approx. 1 week in duration. The symptoms disappeared spontaneously, and in the course of the next year he had transient and intermittent periods of muscular weakness and of "not feeling well". The weakness and constitutional symptoms usually lasted about 4 days, after

which he felt better without having any treatment. After 12 months he had the impression that his lower left extremity was weaker than before. Neurological examination showed no signs of neuropathy. The erythrocyte sedimentation rate was elevated at 37 mm/h. IFA titre for Lyme spirochaetal IgG antibodies was 1 : 128. The total CK was 400 units per liter (normal 37–289 U/l). A deep muscle biopsy from the right quadriceps femoris muscle showed a slight decrease in individual muscle fibre size, but no fibre group atrophy. However, some of the striations were poorly visible. Lymphocytes and plasma cells were found especially near the junction of striated muscle and the subcutaneous fascia, but also between muscle fibres. Electron microscopy could not be done, due to the submission of a very small muscle biopsy specimen.

DISCUSSION

This report confirms that some patients develop clinical symptoms of pain and weakness in muscle groups during the course of *B. burgdorferi* infection. This myalgia and weakness appears to be distinct from the effects incurred from Lyme peripheral neuropathy. Therefore we believe that Lyme myositis is a distinct clinicopathologic lesion, independent of the neuromuscular effects of isolated Lyme-associated peripheral neuropathy. Our experience demonstrates that *B. burgdorferi* myositis can develop very soon after infection (patients 3 and 4), but also months or years later (patients 1 and 2).

In 2 cases, high IgG antibody titres suggest *B. burgdorferi* to be the causative agent of the disease. In the other 2 cases, the *Borrelia* etiology is confirmed by the finding of IgM antibodies against a specific *B. burgdorferi* protein (pC) (Wilske et al. 1986) in case 1 and of positive culture from the skin in case 2. The finding of high IgM antibody titres is unusual in late manifestations of Lyme borreliosis. False positive reactions due to rheumatoid factor (RF) activity were excluded by prior absorption of RF with anti IgG serum (Wilske et al. 1984).

Signs of neuropathy may (patients 1 and 2) or may not accompany the myositis. Including Schmutzhard's patient (Schmutzhard et al. 1986), 4 of the 5 patients suffering from myositis also showed skin involvement at one time or another: erythema migrans in early stages and acrodermatitis chronica atrophicans in later stages. CK may or may not be slightly elevated.

Histopathologically, *B. burgdorferi* myositis has been identified as a focal nodular myositis in the cases 1 and 2, and as merely interstitial myositis in the cases 3 and 4 (Adams et al. 1967; Pongratz and Pilz 1988). Schmutzhard's case and Atlas's cases also fulfilled the criteria of an interstitial myositis. The infiltrates consist of lymphocytes with scattered plasma cells either within the muscle itself, exterior to muscle bundles in the perimysium, or near the fascial junctions and subcutaneous fat. In these few cases we are unable to detect vascular thrombi or vasculitis in the vessels of the muscles. Electron microscopy revealed ultrastructural changes in histiocytes in an activated stage, which are unusual in the dermatomyositis–polymyositis group. High percentages of B and T4 lymphocytes, the low number of cytotoxic T cells and the absence of actual muscle fibre invasion by lymphocytes in inflammatory infiltrations, indicate that, as in dermato-

myositis, *Borrelia* myositis is predominantly due to a local humoral response (Arahata and Engel 1984; Engel and Arahata 1986). It may be a form of autoimmunity initiated by the presence of spirochaetes themselves or an antigen that spirochaetes release during their metabolism. Cultivation of spirochaetes in these muscle biopsies was not successful, but the lack of detection does not exclude the fact that spirochaetes were present in other portions of the muscles of these patients. It is known that these organisms are not found in large colonies, but are randomly distributed in sparse numbers in human tissues. The spherical microparticles in muscle fibres of case 1 are remarkable. This seems to be a unique finding. They probably contain accumulations of cellular debris (Ghadially 1985).

Biopsy findings in patient 2 revealed additional panniculitis and fasciitis. Septal panniculitis in Lyme disease has recently been described by Kramer and co-workers (1986). The fasciitis was not typical of eosinophilic fasciitis (Shulman's syndrome) as common features of this disease, such as pains, a feeling of stiffness, or induration of the skin (Simon et al. 1982), symmetrical involvement of the limbs (Lupton and Goette 1979), accelerated sedimentation rate, elevated serum IgG and eosinophils in the fascia (Simon et al. 1982), were lacking. Hitherto there have been only few reports about fasciitis in *B. burgdorferi* infection. Stanek and co-workers (1987) presented a case of eosinophilic fasciitis. However, Ferradini et al. (1987) doubted that it was really a case of Shulman's syndrome as eosinophilia in the blood and fascia and IgG hypergammaglobulinaemia were absent. Duray (1987), Grahmann et al. (1987), and Sepp and co-workers (1988) reported 3 cases that had some but not all of the features associated with Shulman's syndrome, thus indicating that some hypodermal and fascial lesions in Lyme borreliosis are "Shulman-like", without actually being the syndrome of diffuse fasciitis with eosinophilia.

Both cases tested for human lymphocyte antigens (HLA) were CW3-positive. HLA-CW3 has been proven to be associated with an increased susceptibility to *B. burgdorferi* infection (Pflüger et al. 1988). This may partly account for the exceptional complications of patients 1 and 2. In 3 of our 4 cases, antibiotic therapy cured the clinical signs or the infectious process, but the antibody titres remained reactive. In one case the outcome is unknown.

Lyme borrelial myositis must be taken into consideration, especially if *B. burgdorferi* infection has been proven and the patient complains about localized myalgia, muscle weakness or swelling. Lyme myositis represents another component of a continuously expanding infectious syndrome complex.

NOTE ADDED IN PROOF (Received 26 April, 1989)

After return of the proofs of this paper, one of us (J. de K.), by means of silver staining, succeeded in detecting a few spirochetes in the muscle tissue of our cases 1 and 2. The length of the bacteria was at least 16 μm. Shapes and coilings were the same as those of *Borrelia burgdorferi*.

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Chronic Neurologic Manifestations of Erythema Migrans Borreliosis

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European erythema migrans and North American Lyme borreliosis, like synhilis, affect the nervous system. *B. burgdorferi* as well as related European *Borrelia* strains tend to persist in this organ and induce chronic diseases, as does *T. pallidum*.

Nervous system involvement in the form of meningitis occurs in the second stage of syphilis. During the second stage of tick-borne borreliosis, analogously, we see meningopolyneuritis. In tertiary syphilis, the central nervous system is implicated by parenchymatous inflammation or vasculitis. Recent observations have shown that there exists a tertiary borreliosis which also involves the parenchyma of the central nervous system.[1-4]

This remarkable late neurologic manifestation of *Borrelia* infection shows a disseminated encephalomyelitis. Severe defects are frequent. Because of its nonspecific appearance it remained unknown to us in our sophisticated medical age for a long time. In contrast to syphilis it does not display distinct entities such as tabes dorsalis, general paresis, optic atrophy, or cerebrospinal vasculitis.

For the same reason it can be classified only by its symptomatology as mostly spinal or multiple-sclerosis-like and as mostly cerebral (TABLE 1). We probably still have much to learn about the clinical spectrum. Diagnosis can easily be missed if we do not look for intrathecally synthesized *Borrelia* antibodies. In order to prevent defects, however, early diagnosis and therapy are necessary.

Besides this progressive borrelia encephalomyelitis, we must consider further tertiary manifestations of the nervous system: sensorimotor polyneuritis associated with acrodermatitis chronica atrophicans is well known in Europe. How often the central nervous system is involved simultaneously is still unknown.

As a further tertiary manifestation, we recently observed a latent, mostly subclinical borrelial infection of the nervous system in patients who had had meningopolyneuritis many years earlier.[7]

We report here on 48 cases with tertiary neuroborreliosis, 44 with progressive borrelia encephalomyelitis and four with latent tertiary neuroborreliosis seen between 1985 and 1987 in the Federal Republic of Germany.

MATERIAL AND METHODS

The patients were seen in our clinic or in one of 18 other neurologic departments of the Federal Republic of Germany, which kindly provided us with clinical data.

TABLE 1. Tertiary Neuroborreliosis: Classification

I.	Progressive encephalomyelitis
	A. Mostly spinal (MS-like)
	B. Mostly cerebral (multifocal encephalitis or psychosis)
II.	Polyneuritis (ACA-associated)
III.	Latent infection (subclinical)

Antibodies against *I. ricinus* borrelial strain N 34 were determined by a modified ELISA.[8,9] In order to demonstrate intrathecally synthesized *Borrelia* antibodies, we compared the antibody activity of CSF and serum per weight unit IgG. If a locally synthesized fraction is present the observed CSF value is higher and the serum-CSF difference reflects the intensity of the antibody production in the central nervous system. This method circumvents the calculation of ratios and also takes into consideration the barrier permeability.[10]

RESULTS

Progressive Borrelia Encephalomyelitis

Progressive borrelia encephalitis was diagnosed on the basis of neuropsychiatric findings, inflammatory alterations of the CSF, and in all cases intrathecally synthesized *Borrelia* antibodies. The average age of the 44 patients (24 male, 20 female) was 45.4 years. The youngest patient was 7, the oldest 79 years old. Most of the patients (57%) were in their fifth or sixth decennium (FIG. 1).

At the time diagnosis was made the illness had lasted seven months to 12 years, with a mean duration of 2.8 years (FIG. 2). In seven of the cases the duration was less than 1 year, but in none of the cases less than 7 months. When the infection took place could not be defined in most of the cases. Only five patients (with histories of 9 months

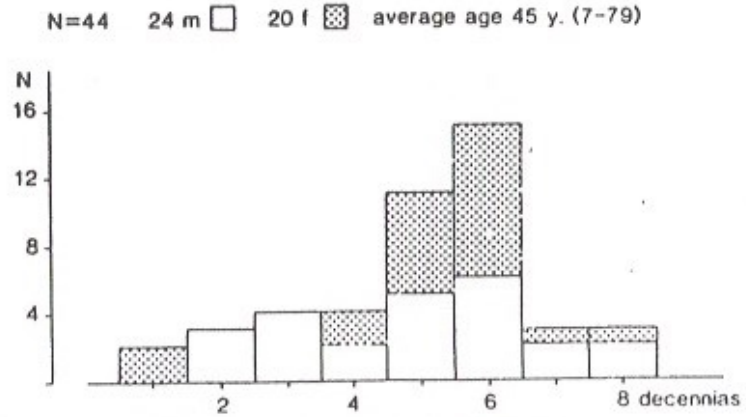

FIGURE 1. Progressive *Borrelia* encephalomyelitis: age duration.

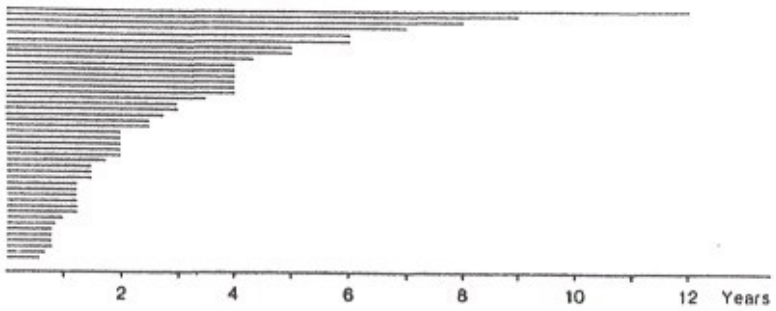

FIGURE 2. Progressive *Borrelia* encephalomyelitis: duration (n = 44).

and 1, 3, 4, or 5 years, respectively) reported symptoms at the beginning of their illness consistent with meningopolyneuritis Garin-Bujadoux-Bannwarth. None of the patients remembered an erythema chronicum migrans or other diseases typical for borreliosis.

The patients frequently complained of gait difficulties, ataxia, bladder dysfunction, visus disorders, hypacusis, or feeble memory and mental concentration. The most frequent wrong diagnoses were tuberculous meningoencephalitis, multiple sclerosis, and viral encephalitis.

Physical examination was normal, with the exception of two male patients 15 and 18 years old who had been sick since ages 5 and 8 years. They both showed retarded growth and sexual development. The older one also showed kyphosis of the spine.

Neurologic examination revealed signs of cranial nerves in 22 of the patients. Retrobulbar neuritis with visus impairment showed in four patients, engorged pupilla with visus deficiency in one patient. Most frequent were facial palsies, mostly unilateral, and impairment of hearing, mostly bilateral, in 12 patients each. Involvement of the n. oculomotorius with diplopia and palsies of the n. glossopharyngicus and n. hypoglossus were rare.

TABLE 2. Progressive *Borrelia* Encephalomyelitis: Clinical Signs (n = 44)

Cranial nerve palsies	
II	5
III	3
VII	12
VIII	12
IX	1
XII	1
Para- and tetraspastic pareses	29
Flaccid pareses	2
Sensibility disorders	9
Bladder dysfunction	11
Ataxia	17
Dysarthric speech	5
Seizures	3
Retarded growth	2
Retarded sexual development	2
Organic mental disorder	14

The most frequent neurologic signs were para- and tetraspastic pareses, which showed in two-thirds of the 44 patients (TABLE 2). Twelve of these 29 patients had only slight pareses, but 17 showed distinct or severe spastic pareses causing gait disturbancies and demanding crutches. Slight hemipareses, mostly transitory, were seen in four cases. In contrast to the motor signs, sensibility disorders were less frequent and mostly only slight. However, one patient showed a distinct sensorimotor transversal syndrome at TH XI with urinary bladder dysfunction. Ataxia (in one-third of the patients) was also a frequent sign, caused in part by spasticity or sensibility disorders. Additionally, however, four patients showed lateral nystagmus and six patients intention tremor. Bladder dysfunction, in some cases combined with bowel dysfunction, showed in 10 of the patients, dysarthric speech in five, and seizures in only three patients.

Organic mental alterations, combined often with neurologic signs, showed in 14 patients. Twelve of these cases had only slight difficulties with memory and mental concentration or showed slight alterations of their affectivity. Only two of the patients had severe mental disorders with dementia-like deficiencies, loss of orientation, and even altered consciousness.

Electroencephalogram was normal or showed only slow waves or slight dysrhythmias. Cranial computer tomogram displayed hypodense foci of different distribution in five of seven cases. Nuclear magnetic resonance showed foci in addition and was positive in all three cases.

TABLE 3. Progressive *Borrelia* Enchephalomyelitis: CSF Findings[a] (n = 44)

Cells (per mm³)	145 (1–566)[a]
Protein (mg/dl)	269 (32–1114)
Antibody titer (per μg IgG)	147 (8–1024)

[a]Expressed as median (range in parentheses).

Mononuclear pleocytosis and impaired blood-CSF barrier were predominant CSF findings (TABLE 3). Cells, mostly lymphocytes and plasma cells and rarely polynuclear cells, ranged from 1 to 566/mm³ with an average value of 145/mm³. Locally synthesized IgG, IgM, and IgA could frequently be demonstrated. Oligoclonal IgG bands could be demonstrated regularly. All 44 patients, including those with normal cell and protein content, showed positive *Borrelia* antibody titer in their CSF.

When antibodies were compared per weight unit IgG in CSF and serum, all patients showed higher *Borrelia* antibody titers in their CSF, indicating the presence of additional antibodies from local synthesis in the nervous system (FIG. 3). The antibody titer in serum per μg IgG ranged from 1 to 128 (mean value 20.8) and in CSF from 8 to 1025 (mean value 91.1). The antibody titer in CSF was one dilution step higher in four cases, two steps in 12 cases, three steps in 21 cases, and four and five steps in three cases each.

The clinical syndromes of the 44 patients are listed in TABLE 4.

After antibiotic therapy, the disorders disappeared only partially. Most of the patients with neuropsychiatric signs before treatment retained to a lesser degree sequelae such as spastic gait, hypacusis, and slight mental disorders.

However, one of the patients with severe mental disorder and dementia-like deficiencies recovered nearly completely and was able to work again as a psychologist. The second patient still has to stay in a psychiatric hospital 2 years after therapy because of his mental condition. In CSF, first cells and then protein become normal. Antibody titer declines more slowly and is often still positive after 1 year.

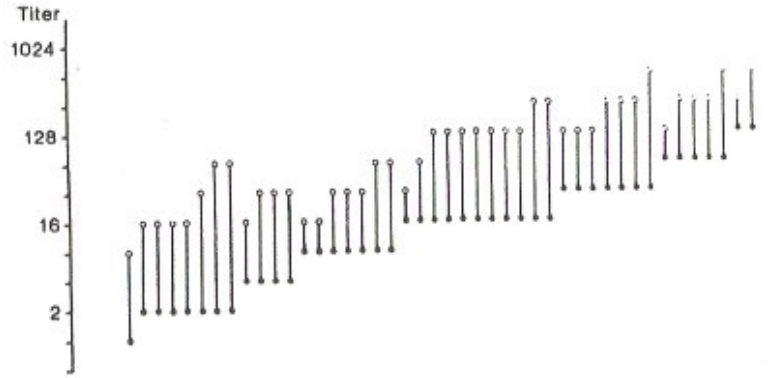

FIGURE 3. Progressive *Borrelia* encephalomyelitis: Antibody titer per microgram IgG in serum and CSF as determined by ELISA ($n = 44$).

Latent Neuroborreliosis

Four patients with latent *Borrelia* infection of the nervous system were detected during a follow-up examination or by chance. Three of them had gone through meningopolyneuritis Garin-Bujadoux-Bannwarth (3, 6 and 12 years earlier) without antibiotic therapy. The diseases had healed by themselves. One patient showed still slight facial palsy, another loss of Achilles reflexes. The fourth patient had complained of migrating pain for 6 years. He did not display any clinical signs. CSF of all four patients showed normal cell count, protein and IgG content, and in particular no intrathecally sythesized IgG as measured by laser nephrelometry. However, all four patients showed two- to fourfold higher *Borrelia* antibody titer per μg IgG in CSF than in serum (TABLE 5).

DISCUSSION

The recently discovered tertiary neuroborreliosis differs distinctly from the well-known meningopolyneuritis Garin-Bujadoux-Bannwarth of the second stage. The early clinically unique manifestation begins 4 to 10 weeks after the infection and heals generally within 4 to 5 months even without antibiotic treatment. Half of the patients remember a tick bite or an erythema. In contrast, borrelia encephalomyelitis begins later and does not heal by itself. The interval between the infection and the onset is difficult to determine because most of the patients do not remember former borreliosis

TABLE 4. Progressive *Borrelia* Encephalomyelitis: Clinical Syndromes ($n = 44$)

Meningitis	34
Myelitis	29
Cranial nerve palsies	22
Encephalitis	18
Mono- and polyneuritis	2

TABLE 5. Latent Neuroborreliosis

Patient Age (y)	Sex	History	Clinical Symptoms	Serum Antibody	CSF Cells (per mm³)	CSF Protein (mg/dl)	CSF *Borrelia* Antibody per μg IgG CSF/serum
59	F	MP[a] 3 y ago	none	750 U	1	42	1024/256[b]
59	M	MP 6 y ago	facial palsy	760 U	2	41	256/32
73	M	MP 12 y ago	Achilles refl. neg.	1600 U	1	53	256/128
71	M	since 6 y ago	migrating pain	145 U	0	51	32/4

[a]Meningopolyneuritis Garin-Bujadoux-Bannwarth.
[b]Reciprocal titer as determined by ELISA.

symptoms. However, five of our patients reported symptoms of a meningopolyneuritis 9 months to 5 years earlier. Obviously pathogenesis is identical with syphilis: infection of the nervous system during the early generalization can persist and evoke severe diseases many years later.

Multilocular symptomatology of progressive borrelia encephalomyelitis resembles many inflammatory, vascular, and neoplastic diseases of the central nervous system. Severe mental disorders can occur that resemble general pareses. More often clinical symptoms such as spinal motor signs, ataxia, bladder dysfunction, slight mental disorders, and in some cases opticus neuritis resemble those found in multiple sclerosis. Contradictory findings, however, are impaired blood-CSF barrier and higher pleocytosis, which are similar to those in tuberculous meningoencephalitis, mycosis, sarcoidosis, neoplastic meningiosis, and neurosyphilis. However, as in neurosyphilis, etiologic diagnosis can be made on the basis of specific CSF antibodies. But in order to prove the activity of the pathogen in the nervous system the presence of intrathecally synthesized antibodies must be demonstrated. Indeed, all our patients showed such autochthonous specific humoral reactions in their CSF, most with high titer.

The utility of CSF findings for diagnosis and evaluation of therapy is well-known from neurosyphilis. Nearly 40 years ago Dattner, a former coworker of Wagner von Jauregg in Vienna, and Thomas postulated activity signs of the CSF when they studied penicillin treatment of neurosyphilis in New York. Because of the similarity of the two spirochetoses, we believe that such indicators are equally important in neuroborreliosis. Half a year after specific therapy cell count should be back to normal. Also, after 1 year CSF protein should be falling or fixed at a low value. In neurosyphilis CSF antibodies persist even after sufficient treatment for several years. How long intrathecally synthesized *Borrelia* antibodies can persist has to be investigated.

Four of our patients showed *Borrelia* antibodies in their CSF as a single finding. Three of them had a borrelia meningopolyneuritis 3, 6, and 12 years ago. Though not treated with antibiotics, all four patients displayed no relevant clinical signs. They also showed no CSF activity, corresponding to the Dattner-Thomas concept. Cells, total protein, and IgG values were within normal range. Therefore one can interpret their CSF *Borrelia* antibody titers as a harmless residual finding. But intrathecally synthesized antibodies additionally present in all cases mean that the pathogen is still active in their nervous system and that the patients have a latent neuroborreliosis.

It cannot be predicted whether this latent infection finally will heal by itself, remain in a stable equilibrium, or relapse at any time. Therefore, those patients should be treated specifically and regularly reexamined.

Our observations demonstrate that intrathecally synthesized antibodies are the most sensitive diagnostic criterion. Using this sign the whole clinical spectrum of tertiary neuroborreliosis can be explored.

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Tick-Borne Meningopolyneuritis *
(Garin-Bujadoux, Bannwarth)

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We studied 100 patients with tick-borne meningopolyneuritis (Garin-Bujadoux, Bannwarth), the neurologic component of European erythema chronicum migrans disease. They had intensive radicular pain, asymmetric polyneuritis combined often with uni- or bilateral facial palsy, lymphocytic meningitis without or with only slight meningismus, and a course lasting three to five months. Neurologic abnormalities were preceded by the bite of a tick or an insect in 37 percent of patients or by an erythema in 41 percent. In addition, many patients had extraneural involvement, such as fever or fatigue. The outcome was favorable in all cases, and occurred faster with antibiotic treatment, but a few patients had slight residual peripheral nervous system deficits.

Tick-borne meningopolyneuritis, which occurs in most European countries, is a clinical syndrome characterized by intense radicular pain, signs of peripheral nervous system involvement, and chronic lymphocytic meningitis. Compared with most non-suppurative infections, the signs and course of this syndrome are unusual. Extraordinary features include the variety and asymmetry of the peripheral nerve involvement, the absence of meningeal signs in most of the cases, and a course of four to six months. These features caused many errors in the discovery of this disease. It was assumed that different presentations were different diseases. In addition, the syndrome was rediscovered several times and given different names such as Paralysie per les Tiques, Meningo-Myelo-Radiculitis nach Zeckenbiss, Polyradiculonévrite atypique avec hyperalbuminorachie et pléiocytose, and Neuro-Radikulo-Meningo-Enzephalo-Myelitis. Only a few authors were aware of a possible causative connection with the preceding tick bite and erythema reported by some of the patients. Today we know that tick-borne meningopolyneuritis is one manifestation of erythema chronicum migrans disease, which is a tick-borne spirochetosis.

Forty years ago the German neurologist Bannwarth [1,2] tried to establish the clinical characteristics of the syndrome. The principal signs were intense radicular pains, lymphocytic meningitis without meningeal signs, and involvement of the peripheral nervous system, particularly facial palsy. He thought that the preceding erythema reported by some of his patients was erysipelas. Therefore, he presumed that the disease had a rheumatic etiology. Peripheral nervous signs often started in the region of the preceding erythema and pain. Bannwarth called the syndrome chronic lymphocytic meningitis with the clinical syndrome of neuralgia or neuritis. None of his patients reported a tick bite.

At the time of Bannwarth's studies, this possible mode of transmission as well as the migrating character of the erythema had already been reported in a local medical

* identical with secondary Lyme neuroborreliosis

journal about a single case from Lyons, France. At the location of a tick bite the man had developed a spreading erythema, intensive pain, peripheral pareses of one arm, and meningitis with a favorable outcome. But this publication by Garin and Bujadoux in 1922 [3] remained unnoticed for decades.

Both Hellerström (1930) [4] and Gelbjerg-Hansen (1945) [5] made the connection between the neurologic syndrome and the preceding erythema which they recognized as erythema chronicum migrans described at the beginning of this century by Afzelius [6] and Lipschütz [7]. Gelbjerg-Hansen recommended that physicians ask patients about preceding tick bite and erythema in all cases of unexplained meningoencephalitis.

Schaltenbrand [8] as well as Bammer and Schenk [9] explained the accentuation of erythema, radicular pains, and multiplex type of polyneuritis, which occurred in the location of the tick bite, as centripetal spreading of the infection along peripheral nerves and lymph vessels. Erbslöh [10] and Wolf [11] emphasized the seasonal appearance of the syndrome in summer and autumn as well as its changing frequency over the years. They believed that these features favored the hypothesis of arthropod transmission.

In 1973, Hörstrup and Ackermann studied the spectrum of this unique syndrome in 47 patients [12]. The signs, symptoms, and course show that the syndrome is a unique nosologic entity. Additional clinical observations during the past ten years [13] have deepened the knowledge about this multifaceted and protracted disease.

METHODS

This report is based on 100 patients seen at the Neurologic University Clinic of Cologne, North Rhine-Westphalia, Federal Republic of Germany, between 1956 and 1983. Sixty-four were male and 36, female. Tick-borne meningopolyneuritis was diagnosed by the presence of prolonged radicular pains, chronic lymphocytic meningitis, and, in most cases, signs and symptoms of peripheral nervous system involvement. Before the etiology of the disease was known, the protracted course and locally produced IgM in the CSF also supported the diagnosis.

RESULTS

General Characteristics

Ages of the patients ranged from 12 to 76 years; peak periods were the third and sixth decades (Fig. 1). Only 27 (27 percent) patients reported a tick bite, 10 (10 percent) an "insect bite," and 41 (41 percent) a preceding erythema. The onset of the ill-

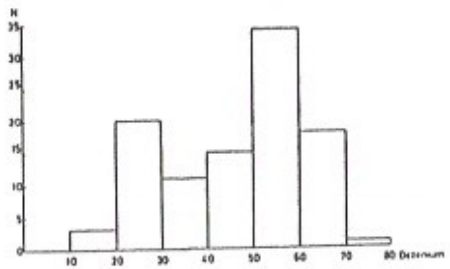

FIG. 1. The age distribution of patients.

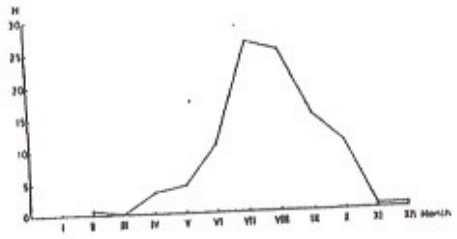

FIG. 2. The seasonal distribution of cases.

ness occurred from February to December, most commonly in July and August (27 and 25 patients) (Fig. 2). Most of the patients came from in or around Cologne. Arthralgia was reported by one patient and another had a severe gonarthritis at the same time as the meningopolyneuritis. Patients often had extraneural involvement such as fever or fatigue.

Radicular Pain and Other Sensory Irritations

At the beginning of nervous system involvement, all but four patients had severe radicular pains, paresthesias, or hyperesthesias, which were the reason for hospitalization in one-fifth of the patients. During the following weeks the pains remained in the same region, involved other regions, or moved completely to other locations.

Peripheral Nerve Lesions

Peripheral nervous system abnormalities often started and were most severe in the region of the pains. They showed no relation to the region of the tick bite and the erythema. Ninety-one of the patients showed motor and 57, sensory lesions (Table 1). Sensory loss was usually less severe than motor. Four of the patients had only sensory signs, and five had no neurologic abnormalities on examination. The lesions developed over a period ranging from days to a maximum of one month, but late recurrences were not seen.

Cranial neuritis was very common (68 patients) (Table 2), and in 28 of the patients was combined with pareses of extremities. Twenty-two of the patients showed

TABLE 1
Pareses and Sensation Disorders

Localization of Pareses	*N*	Additional Sensation Disorders	
		Trunk	Extremities
Cranial nerves	40	5	4
Extremities	22	5	12
Cranial nerves and extremities	28	10	17
Without pareses	9	4	
Abdominal muscles	1		
Total	100	24	33

TABLE 2
Tick-Borne Meningopolyneuritis: Involvement of Cranial Nerves
(N = 68)

Cranial nerves	I	II	III	IV	V	VI	VII	VIII	IX-X	XI	XII
Frequency	–	6	3	1	9	8	63	3	4	3	–

pareses of extremities without cranial neuritis. Most common was facial palsy (63 percent), which was bilateral in 27 cases (Table 2). Slight papilla edema was seen in five of the patients. One had an engorged papilla with hemorrhage. Other cranial nerves were involved less frequently.

The pareses of extremities ranged from mild to severe. In most of the cases, they were distributed asymmetrically (Fig. 3) in the manner of polyneuritis multiplex. They could not be attributed to single nerves. Tendon reflexes were often diminished, sometimes including extremities without pareses. In severe cases, denervation potentials and reduced motor conduction velocity were found during the later course of the disease. Sensory impairment as well as the early sensory irritations were usually distributed asymmetrically and, particularly at the extremities, nonsystemically. All types of sensation were involved, especially superficial sensations.

Meningitis

Only 19 patients had meningismus, often found only on extreme flexion. It was sometimes associated with headache, nausea, vomiting, and photophobia. All other 81 patients were free of meningeal signs. Cerebrospinal fluid analysis showed a pleocytosis of 11 to 906 cells/mm³, mostly lympho-, reticulo-, and plasma cells; total protein was 45 to 360 mg/dl. Among 37 patients investigated by laser nephelometry, locally synthesized IgM could be demonstrated in 29, IgG in 21, and IgA in 12. Spinal fluid abnormalities lasted up to five months (Fig. 4).

Encephalitis and Myelitis

Cerebral involvement was relatively rare. Twenty patients had poor memory, impared concentration, or behavioral changes, and one had slight somnolence. A

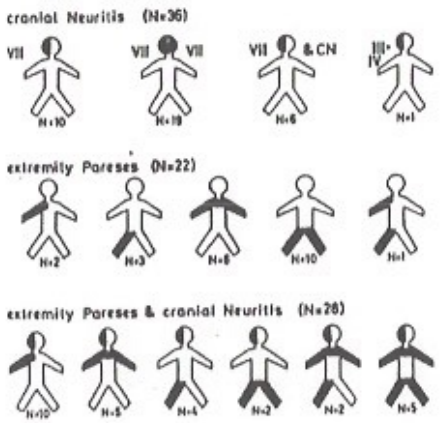

FIG. 3. The distribution of pareses.

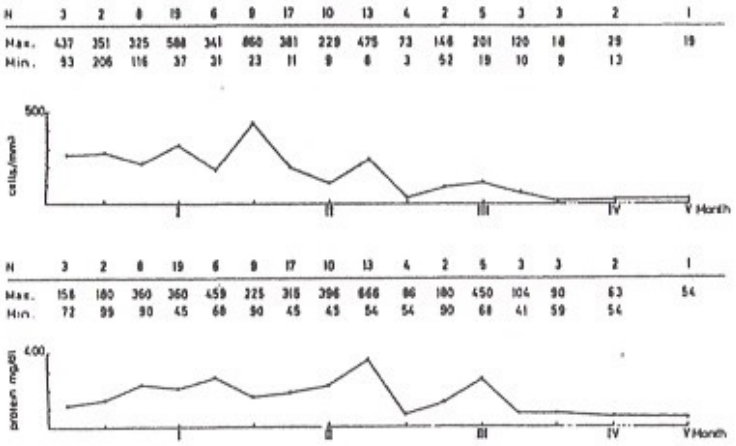

FIG. 4. The median cell count and protein content in CSF of 47 patients.

positive Babinski sign and retention of urine were seen in one patient each. Abnormal electroencephalograms were found in many patients. These abnormalities included generalized slowing or dysrhythmia.

Clinical Course

Erythema, pains, and neurologic signs with meningitis followed the tick bite in a characteristic sequence (Fig. 5). The erythema began a mean of two weeks after the tick bite, radicular pains five and one-half weeks after that, and neurologic signs eight and one-half weeks later. The erythema lasted a mean of one week, pains seven weeks, and neurologic signs and meningitis nine weeks.

The outcome was favorable in all 100 patients. Even severe pareses returned to normal in most of the cases. After several years, only a few patients had slight residual pareses. One patient had a moderate facial palsy after nine years. Eleven patients treated with antibiotics seemed to recover faster from pains and pareses.

Laboratory Findings

Some of the patients had increased sedimentation rates or elevated serum IgM values. Neutralizing tick-borne encephalitis virus antibodies could not be demonstrated in any patients.

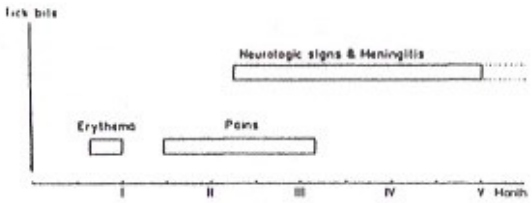

FIG. 5. The sequence of clinical events in tick-borne meningopolyneuritis.

DISCUSSION

Tick-borne meningopolyneuritis can usually be recognized by the neurologic picture alone, but many patients also have a history of tick bite or erythema chronicum migrans, or have locally synthesized IgM in the CSF. It is important to make the correct diagnosis because of the urgency of specific treatment. Our clinical evaluation of 100 patients confirms previous reports of a few or single cases. Based on these series, the common features and wide variety of neurological involvement in this disease are now clear. However, other diseases with polyneuritis multiplex, chronic lymphocytic meningitis, or tick bite must be considered in the differential diagnosis. The determination of antibody titers against the causative spirochete will facilitate the diagnosis and may allow the recognition of additional aspects of this multifaceted disease. For example, cases may exist without CSF alterations or courses may occur that are as chronic as neurosyphilis.

Tick-borne meningopolyneuritis is very similar to the nervous system involvement of Lyme disease; but Lyme disease seems to be more severe, involves the central nervous system more often, and produces longer courses with more recurrences [14].

We could not confirm the hypothesis of centripetal migration of the infection along peripheral nerves. In our experience, the area of peripheral nervous impairment did not occur within the dermatome of the tick bite or the erythema. Today, it is known that the spirochete spreads systemically. However, the pathogenesis of peripheral nerve lesions, which sometimes resemble neuralgic amyotrophia or the vascular forms of polyneuritis, remains unclear.

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Neuro-Ophthalmologic Manifestations of Lyme Disease

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Abstract: Lyme disease is a tick-borne spirochetal infection characterized by skin rash, neurologic, cardiac, and arthritic findings. The authors report six patients with Lyme disease who had neuro-ophthalmologic manifestations. One patient had meningitis with papilledema, two had optic neuritis, and one had neuroretinitis. Three patients had sixth nerve paresis, two of whom cleared quickly, whereas multiple cranial nerve palsies and subsequent optic neuropathy developed in another. Early recognition of neuro-ophthalmologic findings can help in the diagnosis and treatment of Lyme disease.
Ophthalmology 1990; 97:699–706

Lyme disease is a tick-borne illness caused by the spirochete *Borrelia burgdorferi* manifested by skin rash and neurologic and arthritic findings. First described in 1977 by Steere et al,[1] Lyme disease has been increasingly recognized in the Eastern United States as well as certain areas of the Pacific Northwest and Midwest. Although ocular findings of conjunctivitis and symptoms of photophobia were reported in early descriptions of Lyme disease, it is only recently that other ocular manifestations such as keratitis, iritis, and optic neuropathy have been noted. Neurologic involvement in Lyme disease was recognized early as a triad of seventh nerve paresis, meningitis, and radiculopathy. We report six patients with Lyme disease who presented with neuro-ophthalmologic manifestations.

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CASE REPORTS

Case 1. A 6½-year-old boy had a blotchy red rash over both legs, followed by lethargy, headaches, and early morning vomiting. Because of his symptoms, coupled with the presence of a rash, he was thought to have Lyme disease. Lyme titers were sent and the patient was started on intravenous (IV) penicillin. Results of a computed tomographic (CT) scan were normal.

One week later, the patient was seen by an ophthalmologist. Results of examination showed visual acuity of 20/20 in both eyes. Pupils were equal and reacted briskly to light with no afferent pupillary defect. Ocular movements showed a left sixth nerve palsy. Color vision and confrontation fields were intact. Results of external and slit-lamp examinations were unremarkable. Fundus examination results showed bilateral papilledema. Visual field testing was unsuccessful. Spinal tap findings showed an opening pressure of 370 mm of water with clear fluid. The patient was treated with Decadron (dexamethasone) and penicillin; intracranial pressure improved to 190 mm. Magnetic resonance imaging (MRI) findings were normal. IgG and IgM antibody titers were 1:160. The patient was treated with IV penicillin G for 10 days with resolution of the papilledema and left sixth nerve palsy (Table 1).

Table 1. Neuro-Ophthalmologic Manifestations in Patients with Lyme Disease

Case No.	Sex/Age (yrs)	Visual Symptoms	Diagnosis	Systemic Symptoms	Visual Signs	Lyme Titer	ECM Rash	Treatment	Course	Time of Occurrence of Visual Signs and Symptoms after Onset of Lyme Disease
1	M/6½	Diplopia; headache; emesis	Meningitis with papilledema	Headache, lethargy	Visual acuity: 20/20, OU; left sixth nerve paresis; papilledema; ICP, 370 mmH$_2$0	+1:160 IgG	+	8.4 MU IV penicillin daily for 10 days	Complete recovery	1 wk after rash
2	M/25	Blurred visual acuity, OD; headache	Optic neuritis	Back pain, flu-like symptoms	Visual acuity: 20/20+, OD 20/20, OS APD, OD; paracentral scotoma, OD; decreased color, OD	+1:128 IgG	+	Doxycycline, 100 mg orally twice daily	Complete recovery	3 mos after rash
3	M/59	Bilateral sixth/seventh nerve palsies; radiculopathy, optic neuropathy, OD; exposure keratopathy, OS	Chronic cranial nerve paresis with optic neuropathy	Fatigue, malaise, depression, headache	Visual acuity: 20/20, OD 20/25—early, OS 20/400, OD; 20/200—late, OS	+1:6400 IgG	–	Penicillin, Ceftriaxone, Cyclophosphamide, Prednisone	No response to antibiotics; minimal to Cyclophosphamide; died 6 years after onset	2 mos
4	M/16‡	Diplopia	Bilateral sixth nerve paresis	Stiff neck; headache, low back pain	Bilateral sixth nerve paresis with corneal infiltrates	+1:400 IgM +1:1600 IgG CSF IgM 1:200	–	Ceftriaxone, 2 g IV daily	Recovery from sixth nerve paresis with development of left tonic pupil	1 wk
5	F/39	Blurred vision	Optic neuritis	Numbness, left groin and thigh and left fourth and fifth fingers	Visual acuity: First episode, 20/20, OD 20/20, OS Second episode, HM, OD 20/20, OS Bell's OS disc pallor, OS APD, OD	Negative by commercial laboratories; +1:400 IgG +T-cell response test	+	Ceftriaxone, 1 g IV twice daily	Visual acuity: 20/15, OD; 20/25, OS Improved	First episode, 4 mos Second episode, 8 mos
6	F/13	Blurred vision, OD	Neuroretinitis	Headache	Visual acuity 20/50, OU 20/20, OS Blurred discs with exudates in macula	+1:256 IgG, IgM	+	Doxycycline, 100 mg orally twice daily, Ceftriaxone, 2 g IV twice daily	Complete recovery	1 mo

ECM = erythema chronicum migrans; OU = both eyes; ICP = intracranial pressure; IV = intravenous; OD = right eye; OS = left eye; APD = afferent pupillary defect; CSF = cerebrospinal fluid; HM = hand motions; OU = both eyes

Case 2. A 25-year-old man noticed blurred vision in the right eye. Three months previously, he had noticed a rash on the back of his leg associated with multiple headaches and variably intense pain in the back. The patient saw pictures of the Lyme rash and suggested this diagnosis to his physician. An IgG Lyme titer was 1:128. The patient was treated with doxycycline (100 mg orally twice daily). For three days before ophthalmologic examination, he noticed a decrease in light intensity and blurred vision in his right eye. Results of ophthalmologic examination showed that his corrected vision was a poor 20/20 in the right eye and a sharp 20/20 in the left. He had a right afferent pupillary defect with diminished color perception in the right eye. Ocular movements were full. Slit-lamp examination results were unremarkable. Visual fields showed a paracentral scotoma in the right eye; the field was normal in the left eye. Both discs were flat and of normal color. One month later, his visual acuity had improved to 20/20 in both eyes, although he was still aware of some slight impaired color vision in the right eye. No pallor of the optic nerve was noted.

Case 3. A 59-year-old white man had myalgias, sore throat, and malaise, but no fever or rash, while vacationing in Nantucket in August 1982. One month later, a left sixth nerve palsy developed. Results of a tensilon test and CT scan were negative. Three months later, he noticed numbness of both sides of his face, the left side of his tongue, and the fingers of both hands. By November 1983, he complained of progressive fatigue. Results of examination showed bilateral facial nerve paresis and bilateral tongue numbness. Treatment with oral prednisone had no effect. In March 1984, a Lyme titer drawn at his suggestion was positive 1:6400. He was treated with prednisone and IV penicillin G (20 million U daily for a 2-week course) with minimal improvement in his neurologic condition. Attempts at tapering prednisone led to increase in fatigue. In April 1985, the patient was admitted to Yale–New Haven Hospital where he received another 20 million U of IV penicillin G for 3 weeks, but no clear improvement in his neurologic status was noted.

Multiple serum Lyme titers done after treatment showed no change. Cerebrospinal fluid Lyme titer had been positive before treatment, but with no selective concentration. Oligoclonal bands were positive; myelin basic protein was negative.

In April 1985, his visual acuity was 20/20 in each eye. He had bilateral sixth nerve palsies, left greater than right, with bilateral facial nerve paresis. Results of visual field, fundus, and slit-lamp examinations were within normal limits.

Treatment courses with doxycycline, penicillin, prednisone, adrenocorticotrophic hormone, and cyclophosphamide were unsuccessful.

In May 1987, the patient reported a 2-week history of painless, decreasing vision in his right eye. Results of examination showed a visual acuity of 20/30 in the right eye and 20/400 in the left. He had a 1+ afferent pupillary defect in the right and exposure keratopathy in the left. Visual fields showed an inferior defect on the right (Fig 1); the left visual field was normal. By June 9, 1987, his visual acuity was 20/200 in the right eye and 20/400 in the left. He had bilateral sixth and seventh nerve palsies. He again had an afferent pupillary defect in the right eye with further loss of field in the right eye. The left eye was unchanged. Both discs showed pallor, right greater than left.

He was admitted to Yale–New Haven Hospital with left facial numbness, photophobia, diplopia, decreased vision, and paresthesias in both hands. Facial sensation was decreased on the left with marked bilateral facial weakness. Hearing was slightly decreased bilaterally, whereas his gag reflex was decreased on the left side. Moderate weakness of the upper extremities was noted distally on both sides with slight weakness of the left quadriceps.

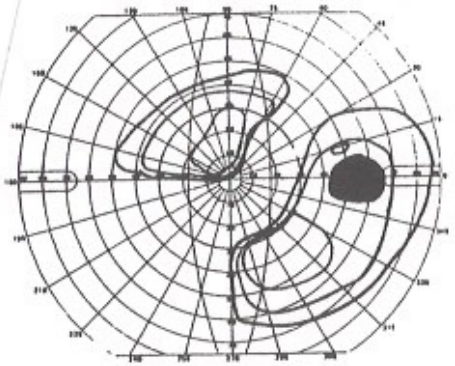

Fig 1. Visual field of the right eye of patient 3 with optic neuropathy developing 5 years after onset of Lyme disease.

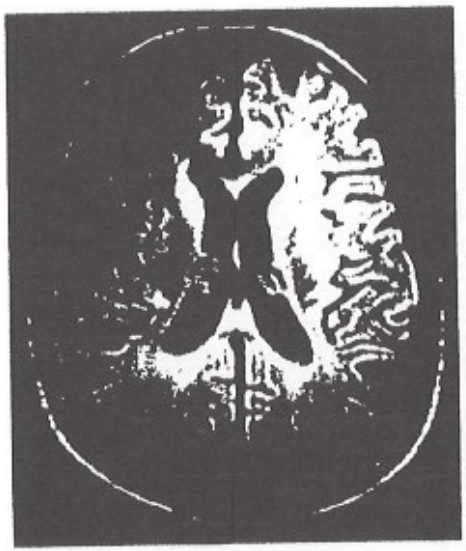

Fig 2. T_1-weighted axial magnetic resonance imaging scan of patient 3 shows multiple areas of periventricular demyelination (TR = 900, TE = 20).

Magnetic resonance imaging of the brain showed multiple areas of white matter disease in the periventricular regions (Fig 2). Cortical volume loss also was noted. No optic nerve or chiasm abnormality was noted. Oligoclonal antibodies were positive. Myelin basic protein was negative.

The patient was treated with cyclophosphamide (150 mg IV every 6 hours), prednisone (60 mg orally daily), and nortriptyline

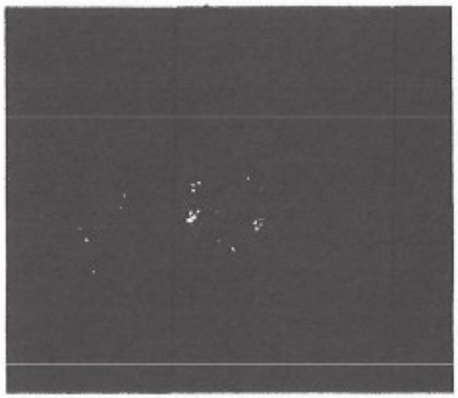

Fig 3. Blurred optic disc in the right eye of patient 6 with neuroretinitis.

(30 mg orally every night). He underwent a left tarsorrhaphy in an attempt to reduce the exposure keratopathy. At the time of discharge, there was no change in neurologic, visual, or mental state.

Case 4. A 16½-year-old boy had horizontal diplopia which was initially intermittent and within 1 week became constant. One week before the onset of the diplopia, a stiff neck, headache, and low back pain developed, all of which resolved after 2 days. No history of tick bite, skin rash, or fever was noted.

Two months previously, pharyngitis, lymphadenopathy, and splenomegaly (with a positive monospot test) developed. He was treated with penicillin for 10 days with resolution of his symptoms.

Visual acuity was 20/20 in both eyes. Both pupils were equal in size and normally reactive. Bilateral sixth nerve palsies were noted. A minimal right hypertropia was noted, most prominent on left gaze. Results of slit-lamp examination showed several subepithelial grayish infiltrates without overlying epithelial abnormalities. No evidence of uveitis was noted. Both optic nerve heads were congenitally full. A lumbar puncture showed 1 erythrocyte and 33 leukocytes (98% lymphocytes and 2% monocytes). Cerebrospinal fluid protein level was 131 mg/dl; glucose concentration was 50 mg/dl. Results of CT scan and MRI were unremarkable. Results of myelin basic protein and oligoclonal bands tests were negative.

Two months after admission, examination results showed normal eye movements. The corneal infiltrates had resolved except for one small central anterior opacity in the left eye. The left pupil was noted to be slightly larger than the right and reacted in a tonic fashion.

Serum titers against *B. burgdorferi* were 1:400 for IgM and 1:1600 for IgG. Cerebrospinal fluid IgM titers were 1:200. He was given a 2-week course of ceftriaxone (2 g IV daily). Within a few days after completing treatment, the diplopia cleared.

Case 5. A 39-year-old woman was bitten by a tick on Memorial Day 1988. Several days after being bitten, the tick was removed from her buttock. Subsequently, a skin rash developed in this location, characterized as erythema chronicum migrans. Lyme titer, tested twice by a commercial laboratory, was negative.

Three months later, low back pain, left Bell's palsy, numbness in the left groin and thigh and left fourth and fifth fingers developed. She was treated with erythromycin for 2 days without relief. Three months later, she was seen in consultation at which time a diagnosis of Lyme disease was confirmed by positive IgG titer of 1:400 along with a positive T-cell response to *B. burgdorferi*. Results of neuro-ophthalmologic examination showed visual acuity of 20/20 in both eyes; however, she had left optic disc pallor. All Ishihara color plates were identified correctly in the right eye, but only 4 of 12 were identified correctly in the left eye. A left afferent pupillary defect was present. Visual fields showed a central scotoma in the left eye. Eye movements showed a bilateral sixth nerve palsy. Results of dilated fundus examination showed that the right eye was normal but the left disc showed pallor. Results of neurologic evaluation showed mild encephalopathy and a spastic left hemiparesis. She was treated with ceftriaxone (1 g IV twice daily for 2 weeks) with substantial improvement. An MRI showed multiple areas of demyelination in the brain stem and cortex with the largest lesion found in the right frontal cortex.

Five months later, sudden loss of vision developed in the patient's right eye, with vision reduced to hand motions. There was now a right afferent pupillary defect; eye movements were full. After another course of treatment with IV ceftriaxone, her visual acuity improved to 20/25 in both eyes. She identified all (except one) Ishihara color plates in each eye. Pupils were equal and reactive; no afferent pupillary defect was noted. Visual fields showed some generalized constriction but no central scotomas. Results of fundus examination showed bilateral optic nerve pallor. Subsequently, her clinical status has remained unchanged.

Case 6. A 13-year-old girl complained of a rash, fever, and arthralgias. With an IgG Lyme titer of 1:256, a diagnosis of Lyme disease was made. The patient was treated with doxycycline. Two months later, headaches developed, and she was noted to have blurred discs. One month later, her visual acuity dropped to 20/50 in the right eye and 20/20 in the left. Results of examination showed blurred discs with exudates in the macula in the right eye consistent with neuroretinitis (Figs 3, 4). She was started on ceftriaxone with complete resolution of headache, return of visual acuity to 20/20, and subsequent improvement in the appearance of the fundus.

DISCUSSION

Lyme Disease is a tick-borne spirochetal illness characterized by three stages that may or may not be present in all patients.[2–4] The illness begins usually in the summer; the first stage includes a skin lesion known as erythema chronicum migrans, often accompanied by a stiff neck, fever, headache, malaise, fatigue, myalgias, and/or arthralgias.[5]

In the second stage, meningitis develops in approximately 15% of patients. A facial nerve palsy develops in approximately one half of those patients. Carditis develops in approximately 5% of patients.[6–9]

In third-stage Lyme disease, months to years after infection, arthritis, which is usually oligoarticular, develops in approximately 60% of untreated patients.[9–12]

In the Northeastern United States, the principal vector is the tick *Ixodes dammini*, but only approximately 30% of persons recall being bitten.[5] The spirochete which causes Lyme disease is *B. burgdorferi*. Tick distribution

and infection rate correlate well with the incidence of Lyme disease.[13,14] Lyme disease has been reported in 43 states and is most commonly seen in the Northeast, upper Midwest, and California.[15,16]

Enzyme-linked immunosorbent assay developed by Pizzarello et al[17] (IgM early, IgG late) is the most common laboratory test for Lyme disease. Laboratory testing, however, is not standardized; therefore, results vary from different laboratories.[18,19] Newer more specific diagnostic tests have been reported (Table 2).[20–23]

Lyme disease may be treated with tetracycline or doxycycline. If there is either no response or if the central nervous system is involved, then ceftriaxone, cefotaxime, or penicillin is recommended.

Central nervous system manifestations are seen both in the second and third stages of Lyme disease.[24–34] Stage II involvement consists of meningitis, cranial neuropathy, and radiculoneuritis alone or in combination.[33] Pachner and Steere[35] evaluated 38 patients with Lyme meningitis. Neurologic manifestations were noted approximately 4 weeks after the onset of erythema chronicum migrans. Eighty-nine percent of the patients had headache, varying in intensity, usually frontal or occipital. Spinal fluid showed lymphocytic pleocytosis, occasional elevation of protein levels, with normal glucose concentration and opening pressure. Fifty percent of the patients had facial palsies (12 unilateral, 7 bilateral).

A peripheral radiculitis, some motor and some sensory, developed in 32%. Other neurologic complications reported include intracranial arteritis and a peripheral neuromyopathy.[27,36]

Third-stage Lyme disease can manifest itself months to years after initial infection. Pachner and Steere[37] studied 26 patients of whom 13 presented with encephalopathy with behavioral changes, memory difficulties, and mood changes. One patient had dementia secondary to Lyme disease with good response to treatment. Six patients had relapsing remitting episodes mimicking multiple sclerosis. Four patients had chronic fatigue, two constant and two intermittent. Meningitis was not always present in these patients and cerebrospinal fluid pleocytosis was noted only occasionally in the third stage. Response to treatment was variable. Investigators also have reported evidence of third-stage Lyme disease in patients with seizure, dementia, myelitis, spastic parapareses, psychiatric disturbances, and ataxia.[38–42]

Eye findings in Lyme disease were first noted in the original observations of Steere et al[1] who noted that approximately 11% of the patients had conjunctivitis and 6% had symptoms of photophobia. In experimental work by Johnson et al,[43] 21 Syrian hamsters were injected intraperitoneally with the organism *B. burgdorferi*. Fourteen days after infection, 47% of the animals had evidence of eye infection. This study, as well as others, suggests that Lyme disease may possibly invade the eye early and then remain dormant. After Duray et al[44] infected seven hamsters with the spirochete, four had positive eye cultures.

Steere et al[45] reported a case of a 45-year-old woman with endophthalmitis secondary to Lyme disease. Initially,

Fig 4. Macular exudates in the right eye of patient 6 with neuroretinitis.

the patient presented with a vitritis which progressed to endophthalmitis; despite treatment with antibiotics and vitrectomy, the eye became phthisical. Subsequently, spirochetes were found in the vitreous. Keratitis has been reported[46–49] with multiple infiltrates at all levels of the stroma. One patient had findings consistent with interstitial keratitis. Smith[50] has seen patients with chronic vitritis, hyperemic optic nerves, and optic neuritis. A 71-year-old man was reported with visual loss associated with headache. Temporal artery biopsy showed findings consistent with giant cell arteritis; subsequent silver stain of the temporal artery biopsy showed spirochetes.[17] Schechter[51] described a 53-year-old man with Lyme disease who had findings consistent with ischemic optic neuropathy. Wu et al[52] reported a 7-year-old boy who had bilateral disc edema with visual acuity reduced to 20/40 in both eyes and a Lyme titer of 1:256.

Farris and Webb reported a 39-year-old black woman with optic neuritis that developed 1 month after treatment for Lyme disease and approximately 2 weeks after treatment with penicillin. This patient had been treated for Lyme disease with a presentation that included aseptic meningitis, bilateral sixth nerve palsy, and a radicular sensory neuropathy. Visual acuity fell to light perception with disc edema. No cells were noted in the vitreous. Three months later, visual acuity returned to 20/50 with evidence of optic atrophy.[53] Optic neuritis has been described in Europe and in the United States.[54,55]

Several cases of pseudotumor cerebri syndrome have been reported in association with Lyme disease.[56,57] In all likelihood, these cases represent meningitis with elevated intracranial pressure rather than true pseudotumor cerebri. Other cases of choroiditis and exudative retinal detachments have been noted.[58] Winwood and Smith[36] reported ocular findings including uveitis, optic atrophy,

Table 2. Diagnostic Aids in Lyme Disease*

Assay	Stage I† Early Disease (ECM, "flu")	Stage II Meningitis and Carditis	Stage III Late Disease	Comment
Antibody ELISA	Frequently negative in first weeks of infection	Approximately 90% positive	Almost 100% positive	Tests both for IgG and IgM with IgM rising early and IgG later; patients with late disease can be seronegative if there has been inadequate early oral antibiotic treatment or if the patient is immunosuppressed
IFA	Frequently negative in first weeks of infection	Approximately 90% positive	Almost 100% positive	(same as above) ELISA preferred because it is more sensitive and specific
Immunoblotting‡ (Western blot)	Frequently negative in first weeks of infection	Almost 100% positive	Almost 100% positive	Electrophoretically separates out different proteins by molecular weight; helpful in differentiating false-positives; not routinely available
Culture	Generally not useful	Generally not useful	Generally not useful	Generally limited in availability to academic centers; *Borrelia burgdorferi* is difficult to grow from sites of infection; culture medium is expensive and not well standardized
T-lymphocyte cell assay‡	Not clinically useful	Not clinically useful	Not clinically useful	Proliferative assay of mononuclear cells to *B burgdorferi* antigens; recent study claiming ability to identify seronegative Lyme has been reported but must still be considered experimental at this time until further corroboration
Urine antigen assay§	Insufficient data	Insufficient data	Insufficient data	Measurement of excretion of antigenic material into the urine may prove helpful, however, no clinical utility has yet been demonstrated
PCR§	Insufficient data	Insufficient data	Insufficient data	The use of PCR to increase the amount of DNA with subsequent use of specific probes to identify bacterial DNA may prove very helpful
Biopsy	Skin biopsy can be characteristic	Brain biopsy has been positive	Joint biopsy is difficult to distinguish from rheumatoid disease	*B burgdorferi* can be hard to identify in tissue sections; usually requires silver stains or immunostains

ECM = erythema chronicum migrans; ELISA = enzyme-linked immunosorbent assay; IFA = immunofluorescent assay; PCR = polymerase chain reaction.

* In central nervous system Lyme disease, cerebrospinal fluid titer can be positive. A negative cerebrospinal fluid titer, however, does not rule out disease if there is a positive serum titer. Should results from serology be unclear or unreproducible, it may be wise to use another laboratory or to send specimens to a laboratory in an academic setting associated with research effort on Lyme disease.

† Diagnosis in the first stage is usually made by examination of the characteristic skin rash (erythema chronicum migrans) and its frequent association with a "flu-like illness," present in an individual living in an endemic area. The percentage of individuals who have early Lyme disease without ECM is controversial but may be as high as 30%.

‡ False-positive serologic results may occur in patients with syphilis, Rocky Mountain spotted fever, autoimmune disease, and other neurologic disorders. Immunoblotting techniques can help distinguish false-positives from other diseases.

§ The T-lymphocyte cell assay, urine antigen assay, and PCR are experimental procedures. Use of information from these tests to manage patients is not recommended.

and Bell's palsy in Caribbean patients with Lyme borreliosis. Lyme disease has been noted in pregnancy[58–60] with at least one case of cortical blindness associated with Lyme disease.[61] An erythema chronicum migrans rash developed in the mother of the child with cortical blindness during the twenty-seventh week of pregnancy. The mother was treated with oral penicillin for 10 days. She had no other manifestations of Lyme disease. The child was full term but had cortical blindness and developmental delay. Another child was born with multiple abnormalities including mental retardation, blepharitis, strabismus, and conjunctivitis.[59]

Neuro-ophthalmologic manifestations in our patients included involvement of cranial nerves VI and VII, optic nerve, and retina. The patients ranged in age from 13 to 59 years. Four of the patients were male, two were female. Three of the patients had blurred vision, whereas three had diplopia. The cases in this report represent a spectrum of the disease—case 3 had involvement of stages II and III, whereas all other patients represented findings of stage II.

Our first patient had meningitis with elevated intracranial pressure, bilateral papilledema, and bilateral sixth nerve paresis. Reports in the literature of pseudotumor cerebri probably represent a similar mechanism, that is, low-grade meningitis rather than true pseudotumor cerebri. Two of the patients with optic neuritis had only a minimal decrease in vision, although one subsequently had a profound decrease in vision in the other eye. In the patient with neuroretinitis with macular star, visual acuity improved and the macular star resolved after treatment. To our knowledge, this is the first patient with neuroretinitis reported with Lyme disease. Three of the patients had sixth nerve involvement—case 1 had involvement secondary to elevated intracranial pressure; case 2 had involvement of bilateral sixth nerve palsy secondary to direct infection; and case 3, the most complicated patient, had involvement of an isolated sixth nerve palsy with no other signs developing for almost 2 months. Cranial nerves VII, IX, X, and XI were involved subsequently in case 3. Years later, an optic neuropathy developed. To our knowledge, this is the first patient with optic nerve involvement in third-stage Lyme disease. Of note, an MRI done in June 1987 showed multiple areas of white plaques around the periventricular region and in the brain stem. Despite multiple courses of treatment, the patient did not improve clinically. This patient represents a rare but dramatic example of the devastating changes from Lyme disease that can occur.

Criteria for determining that these findings can be attributed to Lyme disease include the lack of evidence of other disease, including multiple sclerosis, clinical findings consistent with Lyme disease, the occurrence in patients living in an endemic area, positive serology, and in most cases, response to treatment. Diagnosing Lyme disease and differentiating it from other chronic neurologic disease can be difficult. In some cases, it might be difficult to distinguish between multiple sclerosis and Lyme disease; however, other signs of demyelinating disease after treatment did not develop in any of our patients.

The pathogenesis of the neuro-ophthalmologic findings in Lyme disease may be either immune mediated or secondary to either active infection or vasculitis. The spirochete has been cultured from cerebrospinal fluid[3] and directly from brain parenchyma.[3] Reik[62] pointed out that findings such as the high incidence of hemiparesis and imaging findings of infarction are consistent with vasculitis. To date, however, although endarteritis has been seen in the myocardium and synovium, it has not been demonstrated in the central nervous system. In other cases, immunologic change may be the primary mechanism. Support includes evidence of plaques seen on MRI and evidence of cross-reactivity of neuronal antibodies.[36] Because the patients with optic neuritis and with the sixth nerve palsies responded to treatment, the pathogenesis of their clinical findings was most likely direct infection. In the one patient, however, with a chronic course that included presentation with a sixth nerve palsy and subsequent optic neuropathy, who did not respond to treatment with antibiotic, the mechanism was most likely vasculitis and/or immune mediated.

The findings in these patients should alert ophthalmologists to the possibility that Lyme disease may present as a great mimicker[63] and that signs can include not only facial nerve paresis but also unilateral or bilateral sixth nerve paresis, papilledema, optic neuritis, neuroretinitis, and optic atrophy.

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Bilateral Keratitis in Lyme Disease

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Abstract: Lyme disease, caused by the spirochete *Borrelia burgdorferi*, has ophthalmic manifestations. The authors describe two cases of Lyme keratitis characterized by multiple focal, nebular opacities at varying levels of the stroma which may progress to edema, neovascularization, and scarring. Close observation, in addition to systemic antibiotic therapy, may be sufficient if the visual axis is not involved, and the patient is asymptomatic. Ophthalmology 96:1194–1197, 1989

Lyme disease, distinguished as a separate nosologic entity in 1975, is caused by the spirochete *Borrelia burgdorferi*[1-3] and transmitted by *Ixodes dammini* or related ixodid ticks.[4-8] Illness usually begins in the summer with a characteristic skin lesion, erythema chronicum migrans,[9,10] accompanied by headache, stiff neck, myalgias, fatigue, and lymphadenopathy. Eventually, neurologic[11,12] or cardiac[13] abnormalities and arthritis[9,14,15] may develop.

Conjunctivitis was the most commonly reported ocular complication of Lyme disease in one series[10] with an incidence of 11%. Other ophthalmic manifestations include papilledema with retinal hemorrhages associated with pseudotumor cerebri,[16,17] ischemic optic neuropathy,[18] diplopia associated with oculomotor or abducens nerve paresis,[19,20] bilateral keratitis,[21,22] iritis followed by panophthalmitis,[23] bilateral diffuse choroiditis,[24] and exudative retinal detachments.

We report two additional cases of bilateral keratitis as a manifestation of Lyme disease.

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CASE REPORTS

Case 1. A 25-year-old man, living in Virginia, had febrile meningopolyradiculopathy and Bell's palsy, second- and third-degree heart block, and temporomandibular joint pain in August 1982, 2 months after a tick bite to his navel without apparent local reaction. At that time, he responded to prednisone (60 mg), with total resolution of his right facial palsy although his temporomandibular joint pain persisted on the right side. The prednisone was discontinued in December 1982, and swelling of his left knee developed in January 1983 along with intermittent swelling of his right wrist. Synovial biopsy of the left knee in August 1984 showed inflammation of the synovium and synovial fluid. Lyme titers by enzyme-linked immunosorbent assay (ELISA) drawn in November 1984 at the University of Pennsylvania documented an IgG titer of 1:256 and subsequently 1:512. Quantitative IgM was 110 mg/dl (normal, 60–250 mg/dl); erythrocyte sedimentation rate (ESR) was normal; and antinuclear antibody (ANA), rheumatoid factor (RF), and HLA-B27 were negative. He was hospitalized and treated with 3.3 million units of intravenous penicillin every 4 hours for 2 weeks. In April 1985, an effusion of his right knee developed and he was referred to Yale–New Haven Hospital. The Lyme disease titer by ELISA was IgG 1:1600 and IgM 1:100. His ESR was 8, quantitative IgM was 163 mg/dl, and ANA, RF, FTA-ABS were negative. He was treated with 3.3 million units of intravenous penicillin every 4 hours for an additional 3-week period. His right knee was aspirated. The fluid contained 370 erythrocytes, 5800 nucleated cells, 49 granulocytes, 32 lymphocytes, and 19 tissue cells; it was negative for crystals, had a protein level of 6 mg, a glucose level of 108 mg, and was sterile. During the course of his hospitalization, his Lyme titer by ELISA increased from 1:1600 to greater than 1:6400 although the size of his right knee effusion decreased dramatically. After discharge, his attacks became less frequent and shorter in duration. In February 1987, an effusion of his left knee developed and he was readmitted to Yale–New Haven Hospital and treated with a 3-week course of intravenous ceftriaxone 1 g every 12 hours.

During this second hospitalization, he noticed blurred vision in both eyes with redness and photophobia without discharge. Best-corrected visual acuity was 20/20 − 2 in the right eye and 20/20 in the left. The pupils and results of external examination were normal. The conjunctiva had a few follicles along the superior tarsal border of the superior palpebral conjunctiva and 1+ injection of the nasal bulbar conjunctiva in each eye. Both corneas had multiple focal, nebular opacities with indistinct borders that were peripheral and paraxial but spared the visual axis in each eye (Fig 1). The opacities were seen at different levels in both corneas. Some were restricted to the area of the epithelial basement membrane, whereas others were at varying levels of the stroma including pre-Descemet's. There was no epithelial staining, corneal edema, or neovascularization in either cornea, and the endothelium was unremarkable. The anterior chamber was quiet, and the rest of the ocular examination results were unremarkable. No topical medication was prescribed, and the corneal opacities have waxed and waned without change in visual acuity over a 12-month period.

Case 2. In May 1985, a 7-year-old girl had a swollen right knee 6 weeks after a tick bite, not associated with a skin rash or flu-like syndrome. Her leukocyte count was 12,200, ESR was 61, and ANA was 1:80 with a diffuse pattern. Aspiration of the right knee was turbid with 30,000 leukocytes, 87% of which were polymorphonuclear cells. Lyme disease was diagnosed based on IgG titers of 1:10,240 which later rose to 1:20,480 by ELISA. The patient was treated with 1.5 million units of intravenous penicillin every 4 hours for 3 weeks.

In November 1985, she had decreased visual acuity during school screening. Ophthalmic examination documented the best-corrected visual acuity to be 20/70 bilaterally. Both corneas had multiple focal, nebular opacities with indistinct borders from limbus to limbus (Fig 2). The opacities were subepithelial and at varying levels of the stroma. There was no evidence of edema or neovascularization. The rest of the examination results were unremarkable. No topical treatment was given.

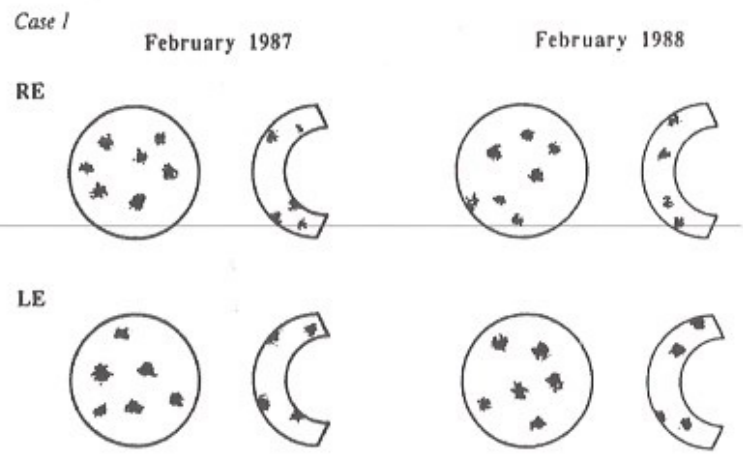

Fig 1. February 1987. Both corneas have multiple focal nebular opacities with indistinct borders at varying levels of the cornea sparing the visual axis. RE = right eye; LE = left eye. February 1988. The lesions have waxed and waned in both eyes without change in visual acuity.

By December 1985, the number of opacities decreased by 50% in the right eye and 90% in the left eye. Best-corrected visual acuity was now 20/30 in the right eye and 20/20 in the left. In February 1986, visual acuity was 20/20 bilaterally. The lesions became fainter and more diffuse involving the visual axis of the right eye and the periphery of the left eye.

Ophthalmic examination results remained unchanged until June 1987 when the patient was seen in follow-up. She had no visual complaints. Her visual acuity was 20/30 in the right eye and 20/20 in the left. There was stromal edema in the superotemporal quadrant extending into the visual axis. A midstromal branching vessel was noted superotemporally (Fig 2). The anterior chamber was quiet, and the rest of the examination results were unremarkable. A corneal scraping was not diagnostic. Results of a VDRL, FTA-ABS, ANA, RF, and tuberculin test were all negative. The patient received topical prednisolone acetate 1% four times daily which was tapered over 5 months. By December 1987, visual acuity was still 20/30 in the right eye with an axial nebular opacity and overlying iron line. Ghost vessels were seen from 10 to 12 o'clock. Visual acuity in the left eye was 20/20 with a few facets in the periphery inferiorly.

DISCUSSION

Our two patients' corneal findings were similar to those previously reported.[21,22] The first patient had multiple focal, nebular opacities with irregular borders at varying levels of the cornea. He did not have corneal edema, neovascularization, or an irregular endothelium as has been previously noted.[22] This patient was not treated with either topical antibiotics or corticosteroids since the visual axis was not involved. During the period of observation, the lesions waxed and waned with no progression of the disease, neovascularization, or edema after 12 months.

The second patient had significant visual worsening in-

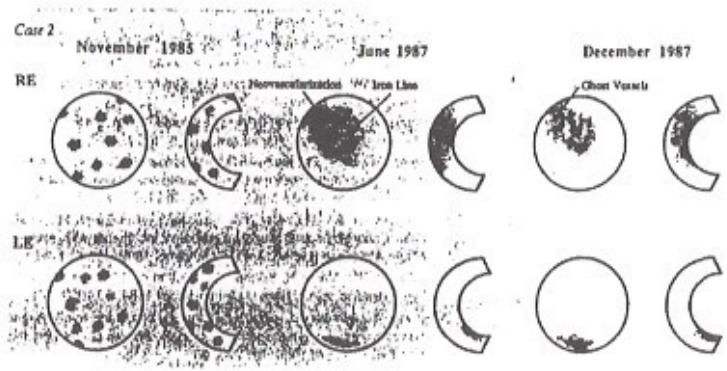

Fig 2. November 1985. Both corneas have multiple focal nebular opacities with indistinct borders at varying levels of the cornea involving the visual axis. June 1987. The right eye (RE) contains a 5-mm area of 1+ stromal edema superotemporally extending into the visual axis. A branching midstromal vessel enters this area at 10 o'clock. The left eye (LE) has an inferior pre-Descemet's opacity. December 1987. RE, a 5-mm ground-glass opacity superotemporally extending into the visual axis with ghost vessels and a central iron line; LE, an inferior pre-Descemet's nebular opacity.

cluding the development of stromal edema and vascularization in one eye. This patient was treated with topical corticosteroids with significant improvement over a 6-month period.

It is clear that Lyme disease has ophthalmic manifestations. Previous experimental studies showed that 45% of hamster eyes were positive for *B. burgdorferi* 14 days after intraperitoneal injection of the organism.[25] A second similar study found positive cultures in 57% of hamster eyes.[26]

We were not able to obtain material from direct histologic examination or culture. We were also unable to determine whether the corneal opacities were the direct result of infection with *B. burgdorferi* or the result of an antigen–antibody reaction or some other immunologic phenomenon in the cornea.

In each case, other causes of keratitis were sought but not found, supporting the theory that the keratitis was secondary to Lyme disease. *Treponema pallidum* is known to produce bilateral diffuse stromal keratitis, usually of a more fulminant nature. There was no evidence of other diseases such as mumps, infectious mononucleosis, or Dimmer's nummular keratitis, which may also produce a somewhat similar interstitial keratitis.

Episodic recurrences of clinical activity in syphilis are believed to be related to persistence of the antigen, either in living sequestered organisms or in fragments of organisms. This may also be true in Lyme disease. In chronic Lyme disease, *B. burgdorferi* persists, inducing an ongoing inflammatory response.[27,28] Several patients who received systemic antibiotics for erythema chronicum migrans reported persistence of symptoms, including joint pain, severe chronic fatigue, numbness of the extremities, and memory loss. In the absence of elevated levels of antibodies to *B. burgdorferi*, these symptoms have been attributed to a post-Lyme disease syndrome rather than considered as evidence of persistence of infection. It has recently been shown that the presence of chronic Lyme disease cannot be excluded by the absence of antibodies against *B. burgdorferi*.[29] A specific T-cell blastogenic response to *B. burgdorferi* may provide evidence of infection in seronegative patients with clinical indications of chronic Lyme disease. Our first patient and a previously reported case of Lyme keratitis[22] were documented initially 5 years after the tick bite or appearance of systemic manifestations of the disease. Lyme keratitis may have been present earlier but was not perceived because the patient was visually asymptomatic and did not seek ophthalmic care.

Our patients' keratitis is similar to those previously reported[21,22]; however, some variation was documented. It appears that Lyme keratitis may progress to edema, neovascularization, and scarring. Close observation, in addition to systemic antibiotic therapy, may be sufficient if the visual axis is not involved, and the patient is asymptomatic.

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European Erythema Migrans Disease and Related Disorders

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European erythema migrans disease, lymphocytoma, and acrodermatitis chronica are a group of disorders associated with the bite of ixodid ticks. These disorders are now thought to be due to a single, or closely related, ixodid tick spirochetes. European erythema migrans disease closely resembles Lyme disease. Serological evaluation may help to separate spirochetal lymphocytoma from other pseudolymphomas of nonspirochetal origin and from lymphoma. Acrodermatitis chronica atrophicans, so far observed mainly in Europe, is presumably a late manifestation of this group of spirochetal disorders.

ERYTHEMA MIGRANS DISEASE (EMD)

Erythema migrans following a tick bite was first described by the Swedish dermatologist Afzelius in 1909 [1]. A few years later, Lipschütz from Vienna gave a more detailed description of another case using the designation erythema chronicum migrans [2]. In 1922, Garin and Bujadoux described a case of meningopolyneuritis [3]. Several years later, Hellerström presented a case with meningitis or, more likely, meningoencephalitis [4]. In 1934, the German dentist Stadelmann included among his six erythema migrans patients the case of a patient with severe joint pain, myalgia, and fatigue [5]. A detailed description of meningopolyneuritis was given by Bannwarth in the early 1940s [6]. In 1951, Hollström observed the beneficial effects of penicillin for both erythema migrans and a patient with meningitis [7]. Binder et al. reported the successful transmission of erythema migrans from human to human four years later [8]. In the 1960s and early 1970s, erythema migrans was recognized as a systemic disease by Hauser and others ([9]; literature in [19]). Hörstrup and Ackermann published a well-defined retrospective study on meningopolyneuritis in 1973 [10]. One year later, a case report showed that low doses of penicillin cleared the erythema migrans but were not sufficient to prevent meningitis; a beneficial effect of high doses of parenteral penicillin was achieved in this patient. In the same paper, it was concluded that a hitherto unknown bacterium must be the cause of both erythema migrans and "erythema chronicum migrans meningitis" [11].

The description by Allen Steere and co-workers of a disease which they first called Lyme arthritis [12] has stimulated further work in Europe. One and a half years before the discovery of the causative organism, high doses of parenteral penicillin or another appropriate antibiotic were suggested for later manifestations of both Lyme disease and erythema migrans disease and for some patients with early manifestations of these disorders [13]. A turning point in the history of EMD and related disorders was the discovery by Burgdorfer and co-workers of a spirochete from ixodid ticks, cultivation of the spirochetes, elicitation of animal lesions, and positive serological reactions in patients with Lyme disease [14]. Recovery of spirochetes from patients with Lyme disease was reported by Steere et al. and Benach et al. a few months ago [15,16]. Ackermann, using *Borreliae,* and other spirochetes, and Neubert, using rodent blood spirochetes supplied by Dr. H.E. Krampitz, obtained positive serological reactions at the same time [17,18]. Soon afterwards, we described 31 patients with what we now call erythema migrans disease [19]. The serological evaluation of 42 patients was presented very recently [20].

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European erythema migrans usually presents as an expanding annular lesion often accompanied by central clearing. This lesion is the hallmark of the disease. Sometimes, a central lymphocytoma-like lesion can also be seen [9,19] (PLATE I). Erythema migrans can disappear after a short duration of up to four weeks; it can exist in its chronic form as erythema chronicum migrans, or it may be absent [19]. European erythema migrans may be accompanied by general symptoms such as headaches, fever and/or fatigue, arthritis or arthralgia, certain neurological findings, probable cardiac involvement, and possibly tracheolaryngitis [19].

To date, we have observed 49 patients; 41 of them have been followed prospectively since December 1978. In our study, 17 patients (35 percent) had joint symptoms; most had involvement of the elbow, the knee, and/or the joints of the fingers. All patients had pain on motion of joints, eight had swelling, and only one experienced redness. Joint symptoms were usually not intermittent. Nine patients (18 percent) had neurologic signs. Six showed clinical evidence of meningopolyneuritis, four had severe headaches, and three were mildly encephalopathic. Seven women (14 percent) had signs suggestive of cardiac involvement. Five experienced one to several attacks of palpitations, one had episodes of substernal chest pain, and one had bradycardia.

Laboratory findings in up to 37 of the 49 patients included a moderate elevation of ESR in 32 percent of the patients (mean value, 16 mm/h), elevation of IgM (13 percent; mean value 316 mg/dl), IgG (10 percent; 1,432 mg/dl), or IgA (3 percent; 394 mg/dl), slight increase of SGPT (19 percent; 26 U/l) or SGOT (6 percent; 21 U/l), and mild cryoglobulinemia in one patient (12.6 mg/dl).

Forty-two patients were evaluated serologically [20]. We found IgG and/or IgM antibody titers against *Ixodes dammini* spirochetes (kindly supplied by Dr. Burgdorfer) to be significantly elevated in only 40 percent of our patients (Table I). Treatment in these patients was begun a mean of eight weeks (0.5-26) after the tick bite or the beginning of the erythema migrans. The highest antibody titers were detected in some patients with more severe disease. Thus, it is possible that antibiotic therapy aborted the antibody response in some patients or that the disease was too mild to allow for significant rise in antibody titer. Seven patients with EMD, three with acrodermatitis chronica atrophicans (ACA), and two with lymphocytoma were also tested at the Rocky Mountain Laboratory for IgG antibodies against both the *Ixodes dammini* and the Swiss *Ixodes ricinus* spirochete. There was no significant difference in the titers between these spirochetes, and the results were basically comparable to those obtained by the Max von Pettenkofer-Institut in Munich [20].

LYMPHOCYTOMA (LYMPHADENOSIS BENIGNA CUTIS)

The first description of a solitary cutaneous lesion with follicles resembling those seen in lymph nodes was published by the Swiss pathologist Burckhardt in 1911 [21].

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Survival of Borrelia burgdorferi in Antibiotically Treated Patients with Lyme borreliosis

Summary: The persistence of *Borrelia burgdorferi* in patients treated with antibiotics is described. The diagnosis of Lyme disease is based on clinical symptoms, epidemiology and specific IgG and IgM antibody titers to *B. burgdorferi* in serum. Antibiotic therapy may abrogate the antibody response to the infection as shown in our patients. *B. burgdorferi* may persist as shown by positive culture in MKP-medium; patients may have subclinical or clinical disease without diagnostic antibody titers to *B. burgdorferi*. We conclude that early stage of the disease as well as chronic Lyme disease with persistence of *B. burgdorferi* after antibiotic therapy cannot be excluded when the serum is negative for antibodies against *B. burgdorferi*.

Zusammenfassung: *Persistenz der Borrelia burgdorferi bei negativer Serologie und Behandlung mit Antibiotika.* Es wird über die Persistenz von *Borrelia burgdorferi* bei sechs Patienten berichtet. Nach dem Zecken- bzw. Insektenstich und Erythema migrans konnte *B. burgdorferi* noch Wochen nach der Antibiotikatherapie nachgewiesen werden. Serologische Befunde waren außer bei einem Patienten negativ. Diese Ergebnisse bestätigen unsere früheren Beobachtungen und sprechen dafür, daß die Antibiotikabehandlung die Antikörperbildung gegen *B. burgdorferi* beeinflussen kann. Ferner zeigen diese Ergebnisse und Beobachtungen, daß nicht nur im Frühstadium der Lyme Borreliose, sondern auch in chronischen Stadien bzw. bei Persistenz des Erregers der Nachweis von Antikörpern negativ bleiben kann.

Introduction

Lyme borreliosis (LB), a multisystem disorder with skin, neurological, cardiac and arthritic symptoms caused by *Borrelia burgdorferi* and predominantly transmitted in Europe by infected ticks, *Ixodes ricinus*, can be diagnosed by the detection of antibodies to *B. burgdorferi* and isolation of the borreliae. The therapy of Lyme borreliosis, especially in the late chronic stage seems to be problematic. Antimicrobial therapy with penicillin G and tetracycline has been recommended. Various treatments especially with penicillin G have been proposed and practiced but none of them has been uniformly effective [1–6]. The last time the cephalosporins, cefotaxime and ceftriaxone have been used with success. We report here about survival of *B. burgdorferi* in patients with Lyme borreliosis after therapy with antibiotics.

Patients and Methods

Patients: Clinical data of our patients are listed in Table 1.
Serological tests: Antibodies to the *B. burgdorferi* in blood and cerebrospinal fluid (CSF) were determined by indirect immunofluorescence test (IFT) as described previously [7]. To avoid unspecific false positive reactions, the test samples were absorbed with *Treponema phagedenis*. Antibody titers ≥ 1:64 are regarded as significantly elevated, titers of 1:32 as borderline.
Bacteriological examinations: The samples of CSF and skin biopsies were examined for *B. burgdorferi* by darkfield microscopy and by culture in MKP-medium as previously described [8]. The cultures were incubated at 33 °C for 5 weeks and examined weekly by darkfield microscopy and subcultures.

Results

Spirochetes were isolated from the culture of CSF and skin biopsy specimens from six patients. The isolates showed typical protein pattern of *B. burgdorferi* in SDS-page. The results concerning the relapse of the disease and reinfection with *B. burgdorferi* after penicillin G and tetracycline therapy in the first case are presented in Figure 1.
Case 1: On July 7, 1985, a five-year-old boy had erythema migrans behind the left ear that faded after three days. A tick bite had never been seen by the parents. Beginning July 25, he had fever of up to 39.4 °C, was more tired than usually and had an erythema in the face, on his upper back and on the upper arms. On August 8 he was admitted to a community hospital with a temperature of 37.9 °C and meningism. CSF analysis showed a lymphocytic pleocytosis (480 cells/µl) and an increase in total protein (86 mg/dl); the electroencephalogram (EEG) was abnormal. Serum IgG and IgM antibody titers against *B. burgdorferi* were 1:64 and 1:128, respectively. Borrelia antibodies were not detected in CSF; culture for *B. burgdorferi* isolation from CSF was not done. The patient was treated with penicillin V orally in a dose of 100,000 U/kg daily for 14 days. On September 2 the CSF contained 26 cells/µl, the protein concentration was 40 mg/dl.
Beginning September 7, a paresis of the left facial nerve appeared that faded almost completely after two weeks. In the CSF, cells increased to 285/µl and protein concentration to 111mg/dl. He then received doxycycline orally in a

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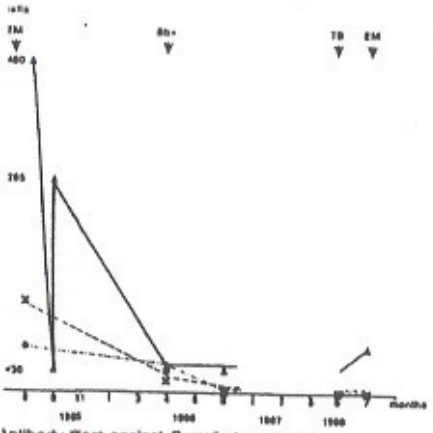
lo 1: Patients with survival of *Borrelia burgdorferi* after antibiotic therapy.

			Antibody titer in Serum IgG	IgM	CSF
. LMR-Bannwarth	Penicillin V 100,000 U/kg – 14 days Doxycycline 2 mg/kg day – 10 days	CSF 7 months a.t.	1:32	1:16	<2
. LMR-Bannwarth	Penicillin G 20 million U/daily – 10 days	CSF 3 months a.t.	1:32	1:64	<2
. LMR-Bannwarth	Ceftriaxone 2 g/day – 10 days	CSF 7.5 months a.t.	n.d.		
. Erythema migrans	Penicillin V 3 million U/daily – 12 days	Skinbiopsy 3 months a.t.	1:128	1:16	
. Erythema migrans	Penicillin G 10 million U/day – 10 days	Skinbiopsy 2 months a.t.	1:32	<1:32	
Erythema migrans	Doxycycline 200 mg/day – 10 days	Skinbiopsy 1 month a.t.	<1:16	<1:16	

= after therapy; *n.d.* = not done.

e of 2mg/kg/daily for 10 days. The CSF gradually be-
ıe normal, but the EEG was abnormal during falling
ep. In April 1986, the boy had a relapse with tiredness,
:r, vomiting, headache and meningism. A new tick bite
not been noted, erythema migrans was missing. The
contained only 20 cells/µl und total protein was 35
dl. Antibody titers against *B. burgdorferi* were in serum
32, IgM 16 and in CSF IgG and IgM <2. EEG was



Antibody titers against *Borrelia burgdorferi*
- – - IgG
- IgM
— Cells
Erythema migrans
Tick bite
- *Borrelia burgdorferi* culture positive

re 1: Persistence of *Borrelia burgdorferi* and reinfection af-
herapy with penicillin V and tetracycline.

again abnormal. *B. burgdorferi* was isolated from CSF after 4 weeks incubation in MKP-medium. The patient was now treated with penecillin V orally in a dose of 200,000 U/kg daily for 22 days. After that CSF protein, cells and electroencephalogram were normal. Cultures for *B. burgdorferi* isolation were not done after the second penicillin V treatment. The IgG and IgM immunofluorescent assay performed in August 1986 was negative in serum and CSF.

In 1988, the patient had a new attack. Two weeks after a tick bite, he had an erythema migrans around the bite site and a painful meningoradiculitis. CSF analysis showed a light lymphocytic pleocytosis (39 cells/µl). *B. burgdorferi* antibody titers in serum and CSF were negative. Culture for *B. burgdorferi* isolation from CSF was not done.

Case 2: A 49-year-old male presented an erythema migrans on the malleolus, 3 days after an insect bite. Typical clinical signs of LMR-Bannwarth syndrome with severe radicular pain and lymphocytic pleocytosis in CSF (144 cells/µl) and increase in total protein (68 mg/dl) began about 7 weeks after the insect bite. EEG was normal. The antibody titers against *B. burgdorferi* in serum at this time were positive (IgG 1:64, IgM 1:256); antibodies were not determined in CSF. Culture for *B. burgdorferi* isolation from CSF was not done.

The patient was treated with penicillin G i.v. in a dose of 20 million U daily over 10 days.

Laboratory investigation of CSF, 4 days after therapy revealed 66 cells/µl and 53 mg/dl protein. Serum IgG antibody titers against *B. burgdorferi* were positive (1:128), the IgM titer was still elevated (1:64). Intrathecal IgG antibody production was demonstrated by significantly elevated CSF/Serum Index (4.2). Culture for *B. burgdorferi* from CSF was not done. Neurological examination was normal, the patient was free of complaints.

Three months later the effect of antibiotic therapy was controlled and neurological examination and CSF examination for white blood cells and total protein were normal.

Antibody titers against *B. burgdorferi* in serum were IgG 1:32, IgM 1:64 and in CSF negative (<1:2) The patient was free of complaints. However, when CSF was cultivated in MKP-medium, *B. burgdorferi* could be isolated.

Case 3: A 26-year-old patient was admitted to our hospital because of headache and intense radicular pain. The radicular pain was most severe at night and located bilaterally in the region of the dermatoma S1 and C7. She reported multiple bites by horseflies a few weeks prior to the admission. Neurological examination was completely normal. Lumbar puncture revealed a lymphocytic pleocytosis with 451 cells/µl. Both total protein (77 mg/dl) and the CSF/serum albumin ratio (10.7) were elevated. Oligoclonal IgG bands were not detected in the CSF. The diagnosis of Bannwarth's syndrome was made although antibodies to *B. burgdorferi* were not detected in serum or CSF. She received ceftriaxone, 2 g/day i.v. for 10 days. During antibiotic therapy, radicular pain and headache improved. Lumbar puncture for the determination of the CSF ceftriaxone concentration was made on the 10th day of therapy 3½ h after antibiotic infusion. The CSF ceftriaxone concentration as measured by HPLC was 1.45 mg/l. At follow-up examination, 7.5 months after antibiotic therapy, the patient reported recurrent episodes of radicular pain, headache, arthralgias and fever. Neurological examination was normal. Antibodies to *B. burgdorferi* were not detected. Repeated lumbar puncture revealed normal values for cell counts (1 cell/µl), total protein (24 mg/dl) and CSF/serum albumin ratio (1.9). Oligoclonal IgG bands were not detected. However, *B. burgdorferi* was isolated from the CSF after 6 weeks incubation in MKP-medium. Erythrocyte sedimentation rate (10/30) and leucocyte counts (7,100/mm³) were normal; C reactive protein, rheumatoid factor and antinuclear antibodies were negative. The patient was treated with cefotaxime 3 × 2 g/day i.v. for 14 days.

Case 4: This, 44-year-old man noticed an erythema migrans of 2 months' duration on the right thigh on June 1, 1988. He had no complaints. His IgG and IgM antibody titers against *B. burgdorferi* were 1:128 and < 1:16, respectively; *B. burgdorferi* could be isolated from skin biopsy taken from the border of the erythema migrans. Treatment carried out with phenoxymethyl-penicillin, 1 million U/3 times daily for 12 days. Erythema migrans disappeared within 2 weeks after the penicillin therapy. Three months later the IgG and IgM antibody titers against *B. burgdorferi* had normalized but *B. burgdorferi* was again isolated from skin biopsy adjacent to the scar of the first biopsy. There were no later manifestations in this otherwise healthy man who could be observed for 7 months. He then received ceftriaxone. Three months after retreatment with ceftriaxone (2 g daily/21 days) a second control culture from a skin biopsy performed adjacent of the first scars was negative.

Case 5: A 40-year-old man developed erythema migrans 24 days after a tick bite, which was slightly pruritic and located on the right arm. Besides a mild itching in the area of the lesion, fatigue and headache, the patient was asymptomatic. The patient received 1 × 10 million U penicillin G for 10 days starting 5 weeks after the tick bite. The erythema migrans faded about 12 days later. Serum IgG and IgM antibody titers against *B. burgdorferi* were negative, cultures for borrelia isolation were not done. Suffering from headache and fatigue 2 months after the disappearance of erythema migrans and 4 months after the tick bite, the patient went to see a doctor. At that time low titre (IgG 1:32, IgM < 1:32) antibodies to *B. burgdorferi* were detected. At our recommendation a skin biopsy of the tick bite area, showing no sign of erythema migrans, was taken. The presence of *B. burgdorferi*, was demonstrated by culturing the organisms in MKP-medium 2 months and 2 weeks after the therapy.

Case 6: On October 20, 1987, a 60 year-old-woman claimed to have had a slowly expanding asymptomatic skin eruption for at least 6 months. There was no history of a tick bite. She had been taking methylprednisolone 4 mg daily for asthma bronchiale for years. In September 1987, she received doxycycline, 200 mg daily for 10 days from her family physician because of a common cold. Physical examination on October 20, 1987, revealed an erythema migrans 32 by 20 cm around both groins. She experienced occasional attacks of palpitations and dizziness, but had been suffering from angina pectoris for years. IgM and IgG antibody titers against *B. burgdorferi* were negative. *B. burgdorferi* could be isolated from skin biopsied from the edge of the erythema migrans on October 20, 1987. ESR and immunoglobulins were normal. The patient refused to take another antibiotic.

Discussion

It is well known that erythema migrans, the most characteristic sign of Lyme borreliosis, tends to disappear without therapy. Nevertheless, antibiotic treatment with penicillin or tetracycline has been recommended in order to prevent subsequent clinical manifestations of Lyme borreliosis [1–6, 20].

Use of penicillin for treatment of Lyme borreliosis was initiated in Europe on the basis of empiric evidence. Therapy today is founded on experiences and studies concerning the favorable effect of penicillin and tetracycline conducted by *Steere* et al. and *Weber* [1–4].

However, some patients later developed symptoms of the disease despite antibiotic treatment [9–11]. Because of these observations it has become questionable if a definite eradication of *B. burgdorferi* with antibiotics is possible. In this context some results of our *in vitro* and *in vivo* studies concerning the susceptibility of *B. burgdorferi* to antibiotics may be of interest [12, 13]. Testing 20 strains of *B. burgdorferi* the MIC_{90} for penicillin G was found to be 4 mg/l. The corresponding result for tetracycline was 0.5 mg/l. These results confirm findings of other researchers [14, 15].

To kill 50% of *B. burgdorferi* with 1.0 µg of antimicrobials we required 48 h using penicillin G and 6–18 h using tetracycline. These differences should be taken into considera-

tion in the therapy of the disease. These results show that effective antibiotic therapy is not only dose dependent, the length of treatment and kind of antimicrobials can be of great importance.

In our *in vivo* experiments with gerbils we could not produce an erythema using intradermal (i.d.) or subcutaneous (s.c.) inoculations. However, we were able to isolate *B. burgdorferi* from the skin biopsy taken 4 cm from the injection site up to 8 months after the infection. The persistence of *B. burgdorferi* can exist in animal tissue and organs for one year and longer. *B. burgdorferi* could be isolated in infected control animals not treated with any antibiotics as well as in animals after treatment with penicillin G (320 mg/kg/day). In contrast, we did not find *B. burgdorferi* in infected animals treated one week with tetracycline (200 mg/kg/day), azithromycin (8 mg/kg/day), imipenem (36 mg/kg/day) and cephalosporins.

Cephalosporins showed a much better antiborrelial effect than penicillin. The highest antiborrelial activity can be seen in the cefotaxime group, the most effective substances were cefotaxime and ceftriaxone.

According to the data of recent clinical studies the cephalosporins are more efficient than penicillin G in late [16, 17], but not in early Lyme borreliosis [21]. *Dattwyler* et al. [17] and *Pal* et al. [11] reported that ceftriaxone and cefotaxime were effective in treating patients with meningoencephalitis and late borreliosis who did not respond to penicillin G therapy.

The CSF concentrations of penicillin G and cefotaxime in our study cefotaxime versus penicillin G [18] demonstrate that cefotaxime penetrates to a greater extent than penicillin G. The CSF levels are evidently above the MIC_{90} values which we determined for *B. burgdorferi*. The concentration of penicillin G did not reach the MIC_{90} in any of our patients.

Data from controlled clinical studies are still scanty, clinical experience is based mostly on a short observation time. Furthermore, proof of a successful therapy is based not only on the disappearance of clinical symptoms but also on the elimination of *B. burgdorferi* and proof is difficult to achieve.

Here we demonstrate the persistence of *B. burgdorferi* in CSF and skin after the therapy with the penicillin G, penicillin V, tetracycline and ceftriaxone. Surprisingly, the isolation of *B. burgdorferi* was possible from the CSF 3–8 months and from skin biopsy 3 months after the antibiotic therapy and disappearance of erythema migrans. Persistent borrelia infection of the CSF was demonstrated by us in a patient with Bannwarth syndrome from the preantibiotic era 10 weeks after the tick bite [19]. In skin biopsy of a treated patient with ACA *B. burgdorferi* could be isolated 3 years after therapy [20]. In untreated patients we demonstrated the presence of *B. burgdorferi* 7 months after the tick bite and 4 months after disappearance of erythema migrans.

In all our treated patients a second – repeated tick – or other insect bite had never been seen, an erythema migrans was not observed. The lack of repeated insect bite and erythema migrans, negative AB-titer against *B. burgdorferi* and negative CSF examination suggest persistence of *B. burgdorferi* rather than reinfection.

How often *B. burgdorferi* may persist in the CSF or skin after therapy or its effect in producing atypical manifestations of disease is not known. The isolation of *B. burgdorferi* from CSF and skin biopsy in our patients after antibiotic therapy with normal CSF-values and negative serological tests for *B. burgdorferi* raises important considerations in the treatment of Lyme borreliosis.

The current recommended penicillin therapeutic regimens would not be expected to assure borreliacidal levels in the CSF as shown by clinical data and our posttreatment isolation of *B. burgdorferi*.

Very interesting is the recurrent episode 7.5 months after ceftriaxone therapy in case no. 3. The antibiotic concentration on the 10th day of the therapy (2 g daily i.v./10 days) 3.5 h after infusion was 1.45 mg/l (MIC_{90} = 0.06 mg/l). Repeated lumbar puncture 7.5 months after therapy revealed normal cell counts, normal total protein and CSF/serum albumin ratio and neurological examination. However, *B. burgdorferi* was isolated from CSF in culture. The reason for the persistence of *B. burgdorferi* in patients after the treatment with antimicrobials is not completely understood. A number of factors may be concerned i.e. stage of disease, virulence of *B. burgdorferi*, insufficient antibiotic therapy, microbial persistence by reduced antibiotic sensitivity and possibility of *B. burgdorferi* survival in tissue, especially in brain tissue and in certain types of cells.

The capacity of *B. burgdorferi* to hide in tissue (heart muscle, eyes, brain) and an insufficient tissue penetration of antibiotics are critical for therapy. Clinical stage of the disease or where *B. burgdorferi* may be present, in heart muscle, eyes or brain, or if there is a uniform pattern, is still unknown.

The central nervous system invasion by spirochetes and a persistence of *Treponema pallidum* after penicillin G therapy is common in neurosyphilis [22, 23].

In view of the hitherto failure of treatment, low CSF concentration of penicillin G, survival of *B. burgdorferi* in patients treated with antibiotics, the moderate penicillin G susceptibility of the organism and unpredictable progression of the disease, it seems appropriate to treat patients with substantially larger doses of antibiotics and/or longer than is provided in present treatment regimens.

Early administration of antibiotics and a 3 to 4 week treatment with 200 mg/daily of doxycycline or 2 g of amoxycillin (stage 1), 3 × 2 g/daily of cefotaxime or 1 × 2 g/daily of ceftriaxone (stages 2 and 3) could probably eliminate the risk of relapse and progression of the disease. Penicillin G cannot be recommended generally, however, if used ≥ 20 million units daily for several weeks are needed. Finally, the effect of therapy ought to be controlled individually by antibody-titer and *B. burgdorferi* culture. As shown, negative antibody-titers do not provide evidence for successful therapy; antibody-titers may become negative despite persistence of *B. burgdorferi*.

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Erratum

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E. Ulrich et al.: "Comparative Efficacy of Ciprofloxacin, Azlocillin, Imipenem/Cilastatin and Tobramycin in a Model of Experimental Septicemia Due to Pseudomonas aeruginosa in Neutropenic Mice", page 311.
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A Randomized Trial of Ceftriaxone versus Oral Penicillin for the Treatment of Early European Lyme Borreliosis

Summary: In a prospective randomized multicenter trial for the therapy of erythema migrans, 40 patients received ceftriaxone 1 g daily for 5 days and 33 patients obtained phenoxymethylpenicillin, 1 million units 3 times daily, for 12 days. Follow-up was for a mean of 10 ± 5 months. Eight oral penicillin recipients (24%) and six ceftriaxone recipients (15%) developed minor consecutive manifestations. Two ceftriaxone and one penicillin recipient(s) still had elevated IgG antibody titers 10 to 20 months after therapy. *Borrelia burgdorferi* could be isolated from the erythema migrans in 29 out of 56 patients (52%) before therapy and in one oral penicillin recipient but none of 24 other patients after therapy. Ceftriaxone was superior to oral penicillin in a subgroup of patients with more than one symptom prior to therapy ($p < 0.01$), but not in the overall evaluation of clinical, serological and bacteriological outcome data. Ceftriaxone ought to be preferred to oral penicillin in patients with more severe early Lyme borreliosis.

Zusammenfassung. *Ein randomisierter Vergleich zwischen Ceftriaxon und oralem Penicillin zur Therapie der frühen europäischen Lyme-Borreliose.* In einer prospektiven, randomisierten Multizenter-Studie zur Therapie des Erythema migrans wurden 40 Patienten mit täglich 1 g Ceftriaxon intramuskulär über fünf Tage und 33 Patienten mit täglich 3 x 1 Mill. I. E. Phenoxymethylpenicillin über 12 Tage behandelt. Die Nachbeobachtung betrug durchschnittlich 10 ± 5 Monate. Acht mit Penicillin (24%) und sechs mit Ceftriaxon behandelte Patienten (15%) entwickelten leichtere spätere Manifestationen. Zwei mit Ceftriaxon und ein mit Penicillin Behandelter wiesen erhöhte IgG Antikörper-Titer 10 bis 20 Monate nach Therapie auf. *Borrelia burgdorferi* konnte bei 29 von 56 Patienten (52%) vor und bei einem Patienten der Penicillingruppe, aber bei keinem Patienten der Ceftriaxongruppe nach Behandlung aus dem Erythema migrans isoliert werden. Ceftriaxon war dem Oral-Penicillin bei einer Untergruppe von Patienten mit mehr als einem Symptom vor Therapie überlegen ($p < 0,01$), aber nicht bei der Gesamtauswertung klinischer, serologischer und bakteriologischer Erfolgsdaten. Ceftriaxon sollte dem oralen Penicillin bei Patienten mit schwererer früher Lyme-Borreliose vorgezogen werden.

Introduction

During the past few years, oral penicillin, tetracycline, erythromycin and amoxicillin have been used in one randomized investigation [1] and in other non-randomized studies [2–5] to treat patients with early Lyme borreliosis. Oral penicillin has not been able to prevent consecutive manifestations of the disease in all patients [1–7] or an infection in an offspring [8]. However, the other aforementioned antibiotics have not definitely been proven to perform better than oral penicillin [1–4]. Tetracyclines tend to prevent "major late manifestations" better [1] and tend to lead to a faster reduction of IgM antibody titers against *Borrelia burgdorferi* within a year [4]. Provisionally, tetracyclines have therefore been recommended as treatment of first choice [1–4]. However, there are also examples of treatment failure among patients treated with tetracyclines [9]. Recent investigations *in vitro* and in animals have demonstrated that ceftriaxone belongs to the most promising antibiotics against *B. burgdorferi* [10–12]. A study in patients with late Lyme borreliosis demonstrated a beneficial effect of ceftriaxone [13]. We wanted to check whether or not ceftriaxone is superior to oral penicillin in early Lyme borreliosis.

Patients and Methods

Patients: From July 1987 until December 1988, patients with erythema migrans seen at the study centers were randomly assigned to one of the treatment regimens. Final evaluation of patients was carried out in early 1989. Erythema migrans was defined as an expanding homogeneous or ringlike erythema of the skin, with or without a history of a tick bite in the center of the lesion [14]. 81 patients were selected. Three patients refused to sign the informed consent, one patient did not comply and four patients had to be excluded because of other, although related diagnoses such as non-specific tick-bite reaction (in one), borrelial lymphocytoma (in two) and initial acrodermatitis chronica atrophicans (in one).

Study centers: (name of the responsible physicians and/or the number of patients seen at each center in parenthesis): Departments of Dermatology, University of Munich (Dr. med. *U. Neubert*; 11), University of Tübingen (Dr. med. *C. Scherwitz*; 7), University of Göttingen (Dr. med. *S. Quadrupp*; 4), University of Düsseldorf (Dr. med. *S. Bottenbruch*, Dr. med. *J. Klose*; 2).

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ndomization: The study centers received blocks with the ran- nly distributed two antibiotics and were requested to strictly ow the rank of order of the randomization schedule. The num- of assigned treatment regimens were stratified for each study ter.

ibiotic therapy: After informed consent was obtained, patients eived either ceftriaxone (Rocephin®, Hoffmann La Roche) 1 g ramuscularly daily on five days (Saturday or Sunday were owed to be skipped) or phenoxymethylpenicillin 1 million its 3 times daily per os for 12 consecutive days. Patients on nicillin were asked to fill out compliance sheets.

aluation of clinical data and follow-up: Patients were seen ior to therapy, and 3 weeks and 3 months after initiation of erapy. Skin lesion and regional lymph nodes were examined d patients were requested to complete questionnaires at these sits. The questionnaire included a detailed list of associated mptoms; only symptoms which could be attributed to Lyme rreliosis were included. Twelve patients were evaluated neuro- gically (n = 5, including lumbar puncture in 3), cardiologically KG, 24-h-EKG, echocardiogramm, n = 5) or rheumatologically = 2) before or after therapy. The study design required the clusion of patients with complications such as established men- goradiculitis or carditis. Some patients had more visits than heduled, but a few skipped one of the follow-up visits. All but ne patient were treated on an outpatient basis. A final telephone terview – the final follow-up – was made by the principal inves- gator in all patients at the end of the study period. The data of he questionnaires were checked at this interview and missing lata were amended; conflicting data were clarified with the hysicians of the study centers. None of the patients was lost to ollow-up. The severity of initial disease was evaluated by count- ng the number of associated symptoms prior to therapy as de- cribed previously [3].

ierology: Prior to therapy, 3 weeks and 3 months after therapy nd if indicated more often, an indirect immunofluorescence test o determine IgM and IgG antibody titers against *B. burgdorferi* was performed in the laboratory of *B. Wilske* as previously de- cribed [15–17]. This procedure included thorough absorption with *Treponema phagedenis*. Antibody titers of ≥ 1 : 64 were considered as positive and those of 1 : 32 as borderline according to a cut-off value above the 98% – and the 95% – percentile, respectively [16]. In this paper, titers of 1 : 32 were counted as significantly elevated.

Bacteriology: (non-mandatory procedure). In 56 patients, a biop- sy from the border of the erythema migrans, 3 to 4 mm in size, was taken before and (adjacent to the scar of the first biopsy) 3 months after therapy. This procedure was performed in local an- aesthesia after disinfection of the skin with 70% isopropanol. The removed skin was immediately placed in modified Kelly medium. Isolation of *B. burgdorferi* was attempted in the laboratory of *V. Preac-Mursic* as previously described [11, 18]. The modified Kelly medium used contained a somewhat lower content of neo- peptone (3 g), glucose (3 g), rabbit serum (5%) and 35% bovine serum albumin (5%) and omitted yeastolate and agar.

Approval: The protocol for this study was approved by the Ethi- cal Committee of the Medical Faculty of the University of Mu- nich. Each study center signed the protocol.

Definitions: Consecutive manifestations were defined as signs and symptoms still present or newly occurring 3 weeks after initiation of therapy and later; they were not called late manifesta- tions because the term late is commonly associated with signs and symptoms of late Lyme borreliosis such as acrodermatitis chroni- ca atrophicans. Definite treatment failure was defined as clear-cut clinical or laboratory evidence that the scheduled antibiotic ther- apy was not effective, meaning persistence or new development of major consecutive manifestations or minor ones (see references 1, 3, 4) in so far as the latter were promptly cured by retreatment, persistence of *B. burgdorferi* or an at least fourfold rise and sub- sequent persistence of the IgG antibody titer at ≥ 1 : 256 for ≥ 6 months; possible treatment failure was assumed when clinical symptoms persisted as minor consecutive manifestations (not cured by retreatment if any) or if antibody titers persisted at ≥ 1 : 256 for ≥ 6 months or at 1 : 32 to 1 : 128 for ≥ 12 months.

Statistical analysis: Differences of quantitative data depicted in Table 1 were analysed by the Mann-Whitney test and qualitative data shown in Tables 2 to 4 by Fisher's exact test. All p values were two-tailed.

Results

Out of our 73 patients with erythema migrans, 31 (42%) had a positive serological test, in 29 patients (40%) *B. burg- dorferi* was isolated from the skin and 44 patients (60%) were serologically and/or bacteriologically positive. Thus, in 29 patients the diagnosis was based on clinical grounds only. Thirteen of the latter group had a history of a tick bite. Associated symptoms prior to therapy included fatigue, headache, arthralgia, myalgia, palpitations, fever, dizziness and a few others in 34 patients (47%). There was a trend that more ceftriaxone recipients compared to oral penicillin recipients had more associated symptoms (p = 0.07; Table 1). None of the patients was severely ill or had es- tablished meningoradiculitis or carditis. The number of pa- tients was unequal among the two therapeutic groups be- cause three patients, later excluded, received oral penicillin and because some study centers treated an uneven number of patients.

Clinical Outcome

Jarisch-Herxheimer reaction, clearance of erythema mi- grans and associated symptoms and the number and dura- tion of consecutive manifestations were not statistically sig- nificantly different in the two groups (Table 1). The sub- group of patients with 2 to 6, but not with 0 to 1 associated symptoms prior to therapy had significantly less consecu- tive manifestations when treated with ceftriaxone compared to oral penicillin (p<0.01; Table 2).

The Jarisch-Herxheimer reaction consisted of fatigue or in- tensification of fatigue in 8 patients, intensification of red- ness and sometimes of subjective symptoms within the ery- thema migrans in 8 patients, fever and/or chills in 3 patients and headache in one patient.

Complete disappearance of the erythema migrans occurred usually within a few weeks. A 50-year-old male ceftriaxone recipient with a six month history of erythema migrans had spontaneous clearing of his skin lesion prior to therapy; *B. burgdorferi* was isolated from normal appearing skin at the site of the previous erythema migrans before but not three months after therapy. Clearance of associated symptoms and signs took place in the majority of patients within the first three weeks after initiation of therapy, usually within the first week. None of our patients became seriously ill or developed definite evidence of meningitis, carditis or other more severe organ involvement.

Consecutive manifestations occurred in several patients. Among eight oral penicillin recipients, five patients de- veloped arthralgia for a median of 12 (range eight to 15) weeks, two patients developed sensory disturbances for a median of 38 [12–64] weeks. A few patients complained of fatigue, sleeplessness, headache and palpitations, respec- tively, for a median of 12 [8–12] weeks. Four out of six ceftriaxone recipients experienced arthralgia for a median of 20 [12–32] weeks and four ceftriaxone recipients (two of them had also arthralgia) developed dizziness, myalgia, tachycardia, palpitations, sensory disturbances and facial palsy (one to three symptoms in individual patients) for a median of 15 [6–28] weeks. There was a statistically signi- ficant correlation between initial severity of disease as measured by the number of associated symptoms (sub- groups of 0–1 versus 2–6) prior to therapy and clinical outcome (p < 0.01; Table 2). This was due to the influence of the group of oral penicillin recipients (p = 0.001), not of the ceftriaxone recipients (no difference). The duration of the erythema migrans prior to therapy had no significant effect on clinical outcome.

Two ceftriaxone recipients experienced remarkable side ef- fects; a 39-year-old man developed a feeling of heat in the mouth, confusion, tachycardia and lowering of blood pres- sure within minutes after the first injection, so that he was then treated with oral penicillin (with no adverse reactions) and a 46-year-old man suffered from febrile enterocolitis for several days, starting on the day following the last injec- tion.

Serological Outcome (see Tables 1 and 4 and Figures 1 and 2)

The median of the elevated IgM antibody titers was 1 : 64 and of the elevated IgG antibody titers 1 : 128 (range 1 : 32

Table 1: Pretreatment and outcome characteristics (n = 73).

Pretreatment characteristics		
Sex: M/F (ratio)	15/18 (0.8)	18/22 (0.8)
Age (y)	46 ± 14	45 ± 15
Size of erythema migrans (cm)	15 ± 10	17 ± 13
Duration of erythema migrans (weeks)	5 ± 8	5 ± 6
Number of associated symptoms	32	50
Patients with associated symptoms (n [%])	11 (33)	23 (58)
Elevated IgM antibody titers (n)[a]	10	11
Elevated IgG antibody titers (n)[b]	4	10
Outcome characteristics		
Follow-up (days)	302 ± 150	324 ± 154
Jarisch-Herxheimer reaction (n)	7	9
Resolution of erythema migrans (days)	10(3–150)[c]	10(3–36)[c]
Resolution of associated symptoms within first 3 weeks (days)	7	9
Consecutive manifestations		
Number of patients	8	6
Number of symptoms	11	10
Duration (weeks)	17 ± 9	16 ± 8
Elevated IgM antibody titers after 4 months (n)	2	2
Elevated IgG antibody titers after 7 months (n)	2	3

There was no statistically significant difference between both therapeutic groups. Numbers indicate mean ± SD unless stated otherwise; a: values of 5 patients developing within 3 weeks after initiation of therapy included; b: value of 2 patients 3 and 9 weeks, respectively, after initiation of therapy included; c: median (range); n = number of patients.

Table 2: Correlation between severity of initial disease and consecutive manifestations; comparison of two subgroups.[a]

Therapeutic groups	Symptoms prior to therapy	Consecutive manifestations (n) No	Yes	p value
Oral penicillin	0–1	24	2	< 0.001[b]
	2–6	1	6	
Ceftriaxone	0–1	24	4	< 0.01[c]
	2–6	10	2	
Both groups	0–1	48	6	< 0.01[c]
	2–6	11	8	

n = number of patients; b: p < 0.01 and c: p < 0.05 if alpha-adjusted according to *Bonferroni*.

Table 3: Number of patients with isolation of *Borrelia burgdor- feri* from the erythema migrans.

	Oral penicillin (n positive/n total)	Ceftriaxone (n positive/n total)
Pretreatment	12/26 (46%)	17/30 (57%)
Posttreatment	1/10 (10%)	0/15 (0%)

The difference between both therapeutic groups was statistically not signi- ficant. n positive = number of patients with positive culture, n total = number of patients in whom a culture was performed, percentage in parenthesis.

ble 4: Number of patients with remarkable outcome events.

		Ceftriaxone (1 g/d) n (%)
nsecutive manifestations	8 (24)	6 (15)
rsistent IgG antibody titer	1 (3)	2 (5)
olation of *Borrelia burgdorferi*	1 (3)	0 (0)
tial outcome (without side effects)	10 (30)	7 (18)[a]
ajor side effects	0 (0)	2 (5)
tal	10 (30)	9 (23)

number of patients; percentage in parenthesis; a = one patient had sistent IgG antibody titer and developed consecutive manifestations.

1 : 512 for IgM and IgG antibody titers, highest value per tient). A transient fourfold rise in IgM antibody titers up 1 : 64 after initiation of therapy occurred in five patients. M and IgG antibody titers persisted for more than four d more than seven months, respectively, in several pa- nts (Figures 1 and 2). Three patients had no serological ntrols.

cteriological Outcome (Tables 3 and 4)

ut of 25 posttreatment controls, *B. burgdorferi* could be olated from a 43-year-old male penicillin recipient three onths after therapy although the erythema migrans had sappeared and the IgG antibody titers had decreased from : 128 to 1 : 32 within three months; three months after treatment with ceftriaxone, a second control culture from a skin biopsy was negative (there were no clinical signs and symptoms before and after therapy).

Repeated Treatment

Ceftriaxone Recipients: A 30-year-old woman had recurrence of erythema migrans and arthralgia eight weeks after the first course of ceftriaxone; she then received 1 g ceftriaxone intramuscularly daily for ten days, but experienced facial palsy, dysesthesia and again arthralgia two weeks after the second ceftriaxone treatment; six weeks later, she received doxycycline 100 mg twice daily for eight days and her symptoms cleared completely within a few days (follow-up 17 months).

Oral Penicillin Recipients: Three patients treated with oral penicillin obtained retreatment (two patients, see bacteriological outcome and Figure 2). A ten-day course of doxycycline 200 mg per day led to improvement of the arthralgia in a 58-year-old woman five months after therapy.

Overall Evaluation

Table 4 summarizes all important outcome events representing definite or possible treatment failures.

Discussion

This open randomized multicenter trial for the treatment of early European Lyme borreliosis has failed to reveal a statistically significant difference between oral penicillin and ceftriaxone regarding an overall evaluation of outcome criteria. However, among a subgroup of patients with more severe initial disease, ceftriaxone reduced the number of consecutive manifestations significantly compared to oral penicillin. Consecutive manifestations are probably the most important clinical criterion of response. All consecutive manifestations observed by us were minor ones according to a previous classification [1] and own experiences [3, 4]. To a certain degree, the findings of this study support the assumption that these minor consecutive manifestations may represent definite or possible treatment failures. So far, none of the antibiotics tested has been able to prevent consecutive manifestations [1–5]. Ceftriaxone as used in the present study has performed similarly in this respect. Accordingly, one of our ceftriaxone recipients experienced, even after prolonged retreatment with the same antibiotic, what appears to be a definite treatment failure since retreatment with doxycycline led to rapid alleviation of all consecutive signs and symptoms.

Certain parameters may have influenced the clinical outcome in our patients. Comparably mild initial disease as commonly found in Europe compared to the United States [14, 19] and benefical effect of early antibiotic therapy may have prevented consecutive manifestations in some of our patients. A long-term follow-up would possibly uncover more cases with consecutive manifestations as exemplified by one of our ceftriaxone recipients who started to develop arthralgia 16 months after therapy. In agreement with two previous reports [1, 3], there was a significant correlation between the severity of initial disease and clinical outcome in our present study. This in turn has increased the chance to find a relatively great number of patients with consecutive manifestations in the subgroup of more severe initial disease.

Persistence of elevated IgG and IgM antibody titers as reported in one of our previous studies [4] was also noted in some of our present patients. Clinical setup before treatment, duration of antibody titer persistence and degree of antibody titer elevation probably play a role in evaluating such cases of presumed treatment failure. One of our oral penicillin recipients (patient a, Figure 2) has had a more than fourfold rise and subsequent persistence of the IgG antibody titer so that one must regard this case as definite treatment failure. Possible treatment failures have been suspected in the other two patients with persistently elevated IgG antibody titers (patients b and c, Figure 2), both of whom received ceftriaxone for long-lasting erythema migrans; one of these patients still had no decline and the other one started to suffer from arthralgia ten and 16 months, respectively, after therapy. These cases show some resemblance to one of our previously observed patients with a persisting IgG antibody titer of 1 : 64 [4] who later turned out to have had meningoradiculitis (*H.-W. Pfister* and *K. Weber*, unpublished observation). Two of our three patients with persistently elevated IgM antibody titers (patients e and f, Figure 1) had a possible treatment failure because of minor consecutive manifestations, but a treatment failure could not be assumed in the third patient because of normalization of the IgM antibody titer after 18 months.

In this investigation, we have also tried to control the success of antibiotic treatment by isolating *B. burgdorferi* after therapy. One of our oral penicillin recipients still had a positive isolate three months after therapy and must therefore be regarded as definite treatment failure although his erythema migrans cleared. In animal studies in which isolation of *B. burgdorferi* was attempted [10, 11], ceftriaxone performed much better than penicillin. We were therefore not surprised about the positive posttreatment culture in one of our penicillin recipients. It was, however, somewhat unexpected that only one single patient remained positive. Had oral penicillin been of no effect, the posttreatment isolation rate should have been about 50% instead of 10% which we have found now, provided other factors such as spontaneous healing could be neglected. The situation among our ceftriaxone recipients was even more clear-cut since none out of 15 patients had a positive culture after therapy.

We found it difficult to evaluate the necessity of retreatment in some of our patients. The decision sometimes depends on rather subjective factors.

If clinical, serological and bacteriological criteria of response are taken together as shown in Table 4, there was no statistically significant difference between the groups. The same statement can be made regarding the occurrence of definite treatment failures; two among oral penicillin recipients (6%) can be compared with one among ceftriaxone recipients (3%). The definite treatment failures uncovered in two of our oral penicillin recipients demonstrated the necessity to follow up patients with early Lyme borreliosis not only with regard to clinical outcome but also by means of appropriate laboratory controls.

We used a relatively short course of five ceftriaxone injections for several reasons. First, animal studies have shown that a five day regimen of daily i. m. injections is sufficient to exert a convincing therapeutic effect [10, 11]. Second, a single daily injection for five days is, although still more inconvenient than oral therapy, relatively easy to tolerate. Third, the cost of this regimen does not appear to be disproportionately high. Fourth, so far there has been no proof of the need to carry out long-term treatment in early Lyme borreliosis. The regimen used turned out to be effective in the majority of our patients. We doubt that higher dosage and longer regimen would have made a significant difference.

Our study has shown that even a short-term course of ceftriaxone is superior to oral penicillin in patients with more severe early Lyme borreliosis and that evaluation of the severity of initial disease can be based simply on the number of associated symptoms. This means that patients with erythema migrans should be carefully checked for associated symptoms prior to therapy in order to decide whether or not an appropriate antibiotic such as ceftriaxone ought to be recommended. Furthermore, we believe that patients with erythema migrans and complications like meningitis should primarily be treated for their complications and therefore be excluded from studies like our present one

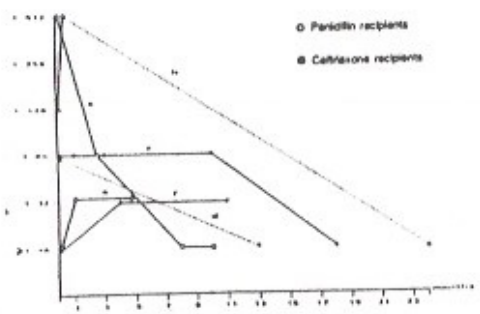

Figure 1: Patients with elevated IgM antibody titer > 4 months after therapy. Patients a–d = no sequelae; e = man, age 28, with arthralgia; f = man, age 64, with muscle tenderness in affected calf starting 6 months after therapy; dotted lines: only a single late serological control available.

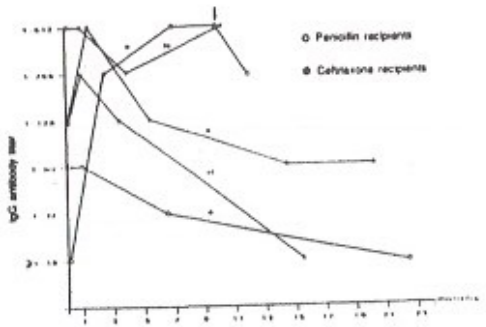

Figure 2: Patients with elevated IgG antibody titer > 7 months after therapy. Patients: a = woman, age 54, no sequelae (same as patient a, Figure 1), arrow: retreatment with tetracycline; b = man, age 71, 3-month history of large erythema migrans, no sequelae; c = woman, age 40, 4-month history of erythema migrans, started to develop arthralgia 16 months after therapy; d = man, age 45, with reinfection, no sequelae; e = man, age 83, no sequelae.

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Although oral penicillin is not definitely inferior to the other oral antibiotics mentioned above, it has not been proved so far that ceftriaxone performs better than these antibiotics in patients with more severe early Lyme borreliosis.

Conclusion

Ceftriaxone should be preferred to oral penicillin in patients with erythema migrans who have two or more associated symptoms prior to therapy.

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TABLE I
Significantly Elevated Antibody Titers by Indirect Immunofluorescence Test in Patients with EMD, ACA, and Spirochetal Lymphocytoma Compared to Controls

		Antibody Titers Against Ixodid Tick Spirochetes			
		IgG		IgM	
Diagnosis	Number of Patients (%)	Unabsorbed 256 (%)	Absorbed with *T. phagedenis* ≥64 (%)	Unabsorbed ≥64 (%)	Absorbed with *T. phagedenis* ≥64 (%)
EMD	42 (100)	7 (17)	11 (26)	19 (45)	14 (33)
ACA	9 (100)	9 (100)	9 (100)	6 (67)*	5 (56)*
Lymphocytoma	4 (100)	2 (50)	3 (75)	3 (75)	1 (25)
Healthy controls	40 (100)	1 (2.5)	1 (2.5)	1 (2.5)	1 (2.5)

*IgM fraction negative

He clearly separated his case from true lymphoma. The term lymphadenosis benigna cutis was introduced by Bäfverstedt in 1943 [22]. Seven years later, Bianchi noticed the beneficial effect of penicillin [23]. In 1957, Paschoud succeeded in transmitting lymphocytoma from human to human [24]. Braun-Falco and Burg noted the polyclonality of the lymphocytes within the lymphocytoma [25]. Histological [26,27], enzyme cytochemical [25,27], immunocytological [25,27–29] and ultrastructural [29,30] studies have provided more insight into our understanding of lymphocytoma and its differentiation from lymphoma in recent years. We recently reported a serological evaluation of patients with lymphocytoma [20].

Lymphocytoma occurs most often as a solitary lesion but several grouped or even more widespread lesions can sometimes be seen. Its size varies from a small nodule to rather large plaques several centimeters in diameter. The red or violaceous lesions have a firm consistency and are sometimes sensitive to touch (PLATE II). The histological diagnosis of lymphocytoma is aided by the follicular arrangement [31]. Such a follicle consists of small lymphocytes and central larger cells some of which represent centrocytes or centroblasts such as are found in true lymph nodes [27]. Unlike lymphoma, B and T lymphocytes are present in lymphocytoma [25,27–29]. Macrophages are present in follicular and non-follicular structures, and a few plasma cells and eosinophils may also be seen [25–27,31]. Electron microscopic studies have revealed the presence of various lymphoid and reticulum cells with many cytoplasmic processes [Weber K: unpublished two cases, 1974; 29,30].

The clinical features and laboratory findings of what we now call spirochetal lymphocytoma are exemplified by the findings in our four patients. All had their lesions on the ear; two-thirds of lymphocytomas are found on the head [9]. Our patients had their lesions for a mean of nine (6–12) weeks. However, if untreated, the lesions may last months and even years. Although our patients had regional lymphadenopathy, general symptoms were absent except for occasional headaches in two. However, meningitis has been reported [32], and a six-year-old boy had six erythema migrans lesions for four weeks. We observed elevations of alpha, globulins in all four patients, beta globulin, in one, and IgM, in another patient (322 mg/dl). Serological examination of our patients revealed that they had a significantly elevated titer of either IgG or IgM antibodies against ixodid tick spirochetes [20] (Table I). Thus, spirochetal lymphocytoma may now be diagnosed serologically.

ACRODERMATITIS CHRONICA ATROPHICANS (ACA)

This condition was first described by the German physician Alfred Buchwald 100 years ago [33]. In 1902, Herxheimer and Hartmann introduced the designation ACA [34]. Jessner described a patient with arthralgia and biopsy-proven laryngitis in 1921 and, three years later, together with Loewenstamm, mentioned 66 patients, nine of whom had joint and bone involvement [35,36]. Soon afterward, Ehrmann and Falkenstein suggested an infectious etiology [37]. In 1942, Kahle reported positive pallida reactions in six out of seven patients; the pallida antigen used was a protein fraction of *Treponema phagedenis* [38]. Two cases were successfully treated with penicillin by Nanna Svartz in Sweden in 1946 [39]. Three years later, Thyresson reported on the successful therapy of 57 cases [40]. Tetracycline, chloramphenicol, erythromycin, and streptomycin were also found to be effective [41–43]. Grüneberg, referring to the report of Kahle, performed pallida reactions in 104 patients, almost 10 percent of whom gave positive results compared to 0.6 percent of the controls; he suspected a group-specific reaction due to a special ACA spirochete [44]. In 1954, Götz reported on the successful transmission of ACA from human to human [45]. Walter Hauser introduced the concept of ACA as a generalized disease. He observed regional lymphadenopathy, reactive hyperplasia in the bone marrow, and electrophoretic changes. Many of his patients gave a history of tick bite, and he found the geographical distribution of ACA to be concordant with the distribution of *Ixodes ricinus*. He was also impressed by the relationship among ACA, erythema migrans, and lymphocytoma [46]. Several cases have been described with both ACA and erythema migrans or erythema migrans-like lesions [43,45,46] and with ACA and lymphocytoma [46]. In addition, in some patients ACA has been found to follow erythema migrans [46,47], and lymphocytoma [48]. Peripheral neuropathy was established as a manifestation of ACA by Hopf in 1966 (cited in [49]). Cryoglobulinemia and changes in the immunoelectrophoresis have been observed in some patients [50–52]. Among the malignancies associated with ACA, monoclonal gammopathy of Waldenström and lymphoma seem to be most remarkable [53,54]. Very recently, we reported the serological findings in six patients [20].

ACA is a chronic disorder usually with characteristic skin lesions [9,55,56]. In the initial stage, the patient has violaceous discoloration and infiltration of the skin, sometimes associated with marked swelling (PLATE III); in the atrophic stage, the skin becomes thin and shows loss of appendages (PLATE IV). The lesions usually spread from distal to proximal sites. In some instances, one finds periarticular fibrous nodules and pseudoscleroderma plaques or bands. Regional lymphadenopathy is common [9,46]. Some patients have peripheral neuropathy [49]. There have been several reports demonstrating joint and bone involvement [35,36,45,55]. Sometimes, patients experience arthralgia before and together with the appearance of the skin lesions; the joint involvement may lead to severe impairment of joint function [36,57]. Hövelborn believed that the same process which caused the skin involvement also affected the joints [57].

Systemic symptoms are usually lacking, but three of our nine patients had symptoms such as fatigue, sensitivity to cold, cough, rhinorrhea, irritability, abdominal pain, and epistaxis during the illness. While skin involvement was present, three of the patients experienced palpitations, dizziness, chest pain and/or syncope (one episode in one patient). Five of the patients had a history of tick bite, but in none did the bite directly precede the appearance of the skin lesions. All patients had skin involvement of the limbs and three of the face. Fibrous nodules were present in three,

regional lymphadenopathy in four, neuropathy in two, arthralgia in one, and a history of erythema migrans in one patient.

Five of nine patients had an elevated ESR (mean value: 31 mm/h); all patients had changes of the protein electrophoresis; four patients had elevation of IgG (1,710 mg/dl) and/or IgM (329), one of IgA (480), and one patient had rheumatoid factor activity without joint complaints. IgG antibody titers against the *I. dammini* spirochete were more or less elevated, but specific IgM titers were insignificant if only the 19S fraction was used or if IgG was first absorbed with an anti-IgG antiserum [20] (Table 1).

In summary, these observations indicate that a single or closely related spirochetes cause a disease with many possible manifestations. The illness may present in its early forms as erythema migrans disease or spirochetal lymphocytoma or both and may later go on to late erythema migrans disease or ACA. Thus, at least in some instances, ACA is thought to be a late manifestation of erythema migrans disease and/or spirochetal lymphocytoma. However, many patients with ACA seem to lack a history of erythema migrans disease or spirochetal lymphocytoma.

THERAPY

We recommend penicillin or tetracycline in appropriate dosage for therapy of European ixodid tick spirochetosis. Erythema migrans can recur after the injection of small doses of penicillin, 300,000 to 600,000 U for two to five days [58,59]; the later manifestations of EMD are not prevented by low doses of oral phenoxymethyl penicillin, 400,000 to 600,000 U for eight to ten days [11,19], and ACA has developed despite injections of procaine penicillin, 300,000 U daily for two or three days [59]. High doses of oral phenoxymethyl penicillin, 1.5 million U three times a day for eight to twelve days, did not prevent arthralgias, but, to date, severe manifestations have not developed in 12 patients with EMD followed prospectively since May 1982 [Weber K: unpublished data]. Intravenous penicillin G, 10 to 20 million U daily for eight to 14 days, were found to be effective in a few EMD patients with meningitis, meningopolyneuritis, and polyarthritis [11,19]. The favorable effect of the tetracyclines, usually 500 mg three to four times a day for seven to ten days, has been observed by many physicians, including ourselves.

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Latent Lyme neuroborreliosis: Presence of *Borrelia burgdorferi* in the cerebrospinal fluid without concurrent inflammatory signs

Article abstract—*Borrelia burgdorferi*, the etiologic agent of Lyme borreliosis, was isolated from the CSF of a patient with elevated serum IgG antibody titers against *B burgdorferi* and a history of multiple tick bites. The absence of concurrent inflammatory signs of CSF as well as intrathecal antibody production indicates a phase of latent Lyme neuroborreliosis in which no tissue infection or reaction has yet occurred. Bilateral tinnitus was the only clinical symptom in this patient. The persistence of the bilateral tinnitus after antibiotic therapy did not support a causal relationship between this symptom and the borrelial infection.

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Lyme borreliosis is predominantly a tick-transmitted disorder caused by the spirochete *Borrelia burgdorferi*. The disease is characterized by various clinical stages including dermatologic, neurologic, cardiac, and rheumatologic manifestations.[1] Neurologic abnormalities, such as Bannwarth's syndrome, meningitis or mild meningoencephalitis, may develop several weeks after a tick bite (stage 2).[2] Months to years later, chronic neurologic disease with progressive encephalomyelitis may evolve (stage 3).[3]

The hallmark of neurologically manifested Lyme borreliosis is lymphocytic pleocytosis within the CSF. Thus far, isolation of *B burgdorferi* from the CSF has been successful only in acute neurologic disease (stage 2) presenting with lymphocytic pleocytosis.[4-6]

We report a case of latent neuroborreliosis that developed in a 17-year-old patient after multiple tick bites. *B burgdorferi* was isolated from the CSF, which was otherwise normal.

Case report. A 17-year-old boy had about 20 tick bites during the months of August through December 1987 while jogging in a forest. This previously healthy patient was admitted to the ENT clinic on December 17, 1987, with bilateral tinnitus that had developed over 2 weeks. Audiography and examination of vestibular function was normal. He was sent to our hospital for a routine neurologic examination, which showed no abnormalities. Indirect immunofluorescence test revealed elevated serum IgG antibody titers (1:64) against *B burgdorferi*, with normal IgM antibody titers (normal, ≤ 1:32, after absorption with *Treponema phagedenis*). The *Treponema pallidum* hemagglutination test was negative. The CSF contained 1 white cell/μl and 21 mg/dl protein. Neither oligoclonal IgG bands in the CSF, as determined by isoelectric focusing, nor intrathecal production of specific antibodies against *B burgdorferi* could be demonstrated. The IgG ELISA was performed.[7] Optical density values were 1.09 in the 1:800 dilution of serum and 1.19 in the 1:2 dilution of CSF. Calculations of the CSF/serum index, which provides a marker for autochthonous intrathecal specific antibody production, were performed as described previously.[8] The CSF/serum ratio for specific antibodies against *B burgdorferi* (RBb) was 0.28%. We used the CSF/serum index calculation based on albumin, because the IgG concentration was below the detection level. The CSF/serum ratio for albumin (RAlb) was 0.21%. The CSF/serum index RBb/RAlb of 1.33 was within normal range, indicating that the antibodies detected in the CSF by ELISA were serum-derived.

When CSF was incubated in modified Kelly medium,[4] spirochetes could be isolated after 4 weeks in the 4th subculture (figure 1). The spirochetes were analyzed by SDS-polyacrylamide gel electrophoresis and Western blot (figure 2). The Western blot was performed with two monospecific polyclonal antibodies anti OspA (PAB OspA/pKo) and anti pC (PAB pC/pKo), and the OspA-specific monoclonal antibody H 5332.[9] For the detection of a common immunodominant 100-kDa range protein of *B burgdorferi*,[9] a monoclonal antibody LA 100 1D4 was used. All tests were performed with the relapsing fever borrelia *B hermsii*, 2 *B burgdorferi* strains (a European skin isolate and the American isolate strain B31), and the CSF isolate of the patient described in this report. This major OspA component may be absent in European isolates but European strains may express a major protein in the 20-kDa range (pC). The protein pattern of the CSF isolate is very similar to the *B burgdorferi* skin isolate representing only a major pC. The monoclonal antibody H 5332 was not reactive by Western blot with the 2 European *Borrelia* isolates (results not shown), as previously reported also on isolates from other European patients with typical clinical manifestations of Lyme borreliosis.[9] *B hermsii* did not react with PAB OspA/pKo or PAB pC/pKo, whereas the 3 other borreliae reacted positively with at least 1 of these antibodies. Positive reactivity with at least 1 of these monospecific polyclonal antibodies has been used for identification of H 5332 negative *B burgdorferi* strains.[9] In addition, positive reactions with MAB LA 100 1D4 were also shown for both *B burgdorferi* strains and the CSF isolate; in contrast, MAB LA 100 1D4 did not react with *B hermsii*. This antibody MAB LA 100 1D4 was also negative with other relapsing fever borreliae (*B duttoni*, *B turicatae*, *B parkeri*) (Wilske et al, unpublished data). These results confirm that the CSF isolate is *B burgdorferi* and not a relapsing fever borrelia. The patient was treated with cefotaxime, 3 × 2 g per day intravenously over 5 days.

Figure 1. Borrelia burgdorferi *(strain PBo) isolated from the CSF after incubation in modified Kelly medium (fuchsin stain, ×1,200 before 63% reduction).*

Three months later (April 8, 1988) the patient reported persistent bilateral tinnitus. Again, neurologic examination was entirely normal. Repeated lumbar puncture revealed 2 white cells/μl and 23 mg/dl protein without demonstration of oligoclonal IgG bands or intrathecal production of antibodies against *B burgdorferi*. CSF cultures were negative. Serum IgG antibody titers against *B burgdorferi* were still elevated (1:64), and IgM antibody titers were normal.

Discussion. Isolation of *B burgdorferi* from the CSF of patients with neurologically manifested Lyme borreliosis has been achieved in only a few cases. *B burgdorferi* has been isolated from the CSF only in acute

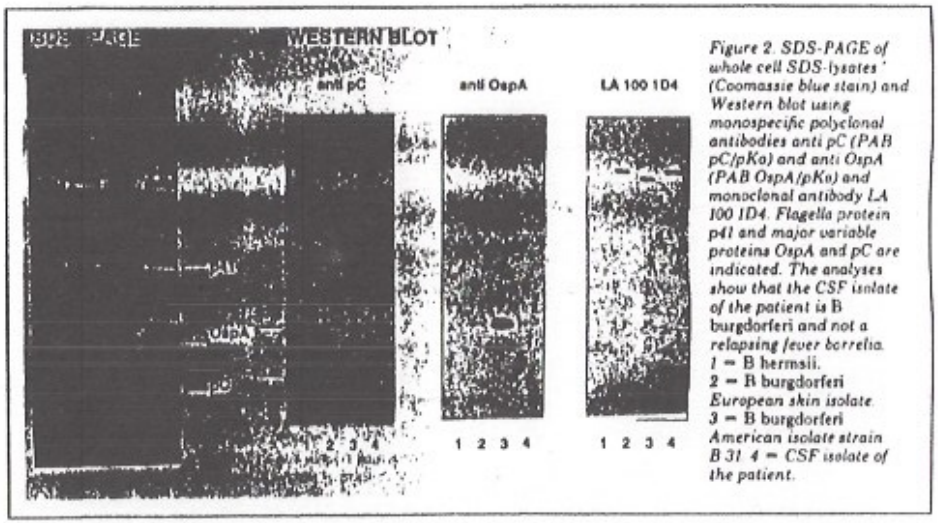

Figure 2. SDS-PAGE of whole cell SDS-lysates (Coomassie blue stain) and Western blot using monospecific polyclonal antibodies anti pC (PAB pC/pKo) and anti OspA (PAB OspA/pKo) and monoclonal antibody LA 100 1D4. Flagella protein p41 and major variable proteins OspA and pC are indicated. The analyses show that the CSF isolate of the patient is B burgdorferi *and not a relapsing fever borrelia.*
1 = B hermsii.
2 = B burgdorferi *European skin isolate.*
3 = B burgdorferi *American isolate strain B 31.*
4 = CSF isolate of the patient.

neurologic manifestations of Lyme borreliosis associated with lymphocytic pleocytosis. Isolation of borrelia from the CSF of a patient with Lyme meningoencephalitis[1] and of patients with Bannwarth's syndrome and Lyme meningitis have been reported.[4,6] Persistent borrelial infection of the CSF was demonstrated in a patient with Bannwarth's syndrome from the preantibiotic era, even though the patient's clinical condition had improved.[10] Marked lymphocytic pleocytosis was still present in the CSF at the time of the second borrelial isolation.

We report the isolation of *B burgdorferi* from the CSF of a patient with otherwise normal CSF findings. The history of multiple tick bites and the demonstration of elevated serum IgG antibody titers against *B burgdorferi* prompted us to look for borrelial infection of the CNS. Surprisingly, *B burgdorferi* could be isolated from the CSF in the absence of any concurrent inflammatory changes. We consider this clinical setting to be consistent with a "latent Lyme neuroborreliosis." Late neurologic manifestations resembling neurosyphilis may develop in Lyme borreliosis.[3] These chronic neurologic manifestations have been reported with and without previous stage 2 neurologic disease.[3] Latency periods of many years after the primary infection seem to be possible. We suppose that our patient may have been at the beginning of this latency period, in which no tissue infection or reaction had yet occurred.

It is difficult to decide whether the patient's bilateral tinnitus may be attributed to borrelial infection. However, the persistence of tinnitus despite antibiotic therapy argues against a causal relationship between the tinnitus and the presence of *B burgdorferi* in the CSF.

In conclusion, we could demonstrate the presence of *B burgdorferi* in the CSF of a patient with elevated serum IgG antibody titers against *B burgdorferi* and a history of multiple tick bites. The absence of pleocytosis, protein elevation, oligoclonal IgG bands, and specific antibody production within the CSF indicates latent Lyme neuroborreliosis.

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Demonstration of Locally Synthesized Borrelia Antibodies in Cerebrospinal Fluid

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Summary

Antibodies against *Borrelia burgdorferi* develop slowly. Low titers can be anamnestic. In order to prove the etiology of manifestations of erythema chronicum migrans disease of the nervous system like meningopolyneuritis Garin-Bujadoux-Bannwarth or progressive borrelia encephalomyelitis we used the ELISA to measure specific IgG antibodies against *Ixodes ricinus* borrelia per µg IgG in serum and cerebrospinal fluid.

With the mentioned method we were able to demonstrate locally synthesized antibodies in the cerebrospinal fluid. Until the 110th day of illness a difference between serum and CSF in favour of the latter as high as five binary dilution steps could be found. Later on in time the difference decreased to four dilution steps or less.

Introduction

It is difficult to establish the diagnosis of erythema chronicum migrans disease, if clinical symptoms are not characteristic. Since borrelia infections occur with rather high incidence and the course can be clinically latent, a positive antibody titer is no evidence for the etiology of a recent disease.

There are the same difficulties as in dermatology to diagnose the infections of the nervous system. The common meningopolyneuritis (Garin-Bujadoux-Bannwarth) can show an atypical course, so that the other polyneuritis and chronic lymphocytic meningitis have to be taken into consideration.

The newly observed long-term disease, progressive borrelia encephalomyelitis, differs in symptoms and course from the meningopolyneuritis to a large extent. Their signs are even pointing to a multiple sclerosis or sarcoidosis of the nervous system. In those cases it proved to be useful to determine antibodies in the cerebrospinal fluid in order to establish the diagnosis of a borrelia infection of the nervous system. Antibodies synthesized locally in the nervous system refer to an infection of this system.

Material and Methods

We used a modified ELISA (2) to measure IgG antibodies against *Ixodes ricinus Borrelia* in sera and cerebrospinal fluids. For the antigen preparation *Ixodes ricinus Borreliae*, strain N 34, originally isolated from *Ixodes ricinus* ticks in the Federal Republic of Germany, were grown in modified Kelly's medium. The organisms were harvested by centrifugation, washed several times

and sonicated in ice water. After filtration this lysate was used as antigen for solid-phase coating.

The optimal antigen concentration was determined by checkerboard titrations of twofold dilutions of antigen and of a known high-titered antiserum. The antigen was stored in aliquots at –20 °C.

We coated the wells with antigen, 100 µl/well suspended in a coating buffer, and stored the plate covered at +4 °C overnight. The next day we prepared binary dilutions of sera and cerebrospinal fluids, using PBS/Tween, starting with the dilution 1 mg/100 ml (that means 1 µg/well). Total IgG levels of the samples were determined by laser nephelometry (3, 4). The 96-wells Microtitration plates were washed three times with PBS/Tween, then we added 0.1 ml aliquots of the diluted sera and cerebrospinal fluids to each well. After an incubation time of 45 min. at 37 °C, the plates were washed three times again, then 0.1 ml of anti-human IgG-alkaline Phosphatase conjugate, 1:500 diluted in a buffer, recommended by SIGMA, was appended. After 45 min. incubation time we added SIGMA 104 phosphatase substrate tablets, diluted in ELISA substrate buffer, containing magnesiumchloride and diethanolamin. After renewed incubation of 45 min. the reaction was stopped by the addition of 0.05 ml of 3 N sodium hydroxide. The plates were read immediately in a minimicro-ELISA-reader (Fa. Dynatech) at 410 nm wave-length. The endpoint titers of the patient's sera and spinal fluids were determined at optical density values that were 2 standard deviations above those of chequed series of normal control sera and spinal fluids.

Results

I. Meningopolyneuritis (Garin-Bujadoux-Bannwarth).

We investigated the borrelia antibody response of 109 sera and 95 cerebrospinal fluids (CSF) of 33 patients during a time span from 4 days to 8 months. All the samples gave positive results with the exception of one cerebrospinal fluid specimen, which until the 28th day of disease was the only negative one besides 23 positive samples.

The examined sera had antibodys titers between 1 and 64 per 1 µg IgG, the cerebrospinal fluids were between 4 and 512 per 1 µg IgG. The first figure shows the serum- and cerebrospinal fluid-titers of a 54-years-old patient during a period of 4 months.

Already at the beginning of the neurological disease we found elevated antibody titers in the sera and spinal fluids. We observed a fourfold increase of titers in both kinds of samples in 6 cases.

Figure 2 shows the average values of the serum- and spinal fluid-titers per 1 µg IgG and homogenous, but a different high course of the titers.

The antibody titers in the CSF were 1–5 binary dilution steps higher than in the sera. With the exception of 3 cases during the first 28 days of the disease, the cerebrospinal fluids showed higher titers than the associated sera. Even between the 5th and the 8th month of illness 9 patients exhibited antibody titers in CSF 1–4 binary dilution steps higher than in serum.

Figure 3 represents the average values of differences, expressed in binary dilution steps, between serum- and cerebrospinal fluid-titers over a period of 8 months.

II. Progressive Borrelia Encephalomyelitis

We examined 42 pairs of sera and CSF from 18 patients during a period from 9 months to 12 years. All the samples gave positive results.

The serum titers per 1 µg IgG ranged from 1–256, the spinal fluid titers from 8–512. At every point in time during the disease, we observed high titers in sera and cerebrospinal fluids. In all cases the antibody titers of CSF were 1–6 binary dilution steps higher than in serum.

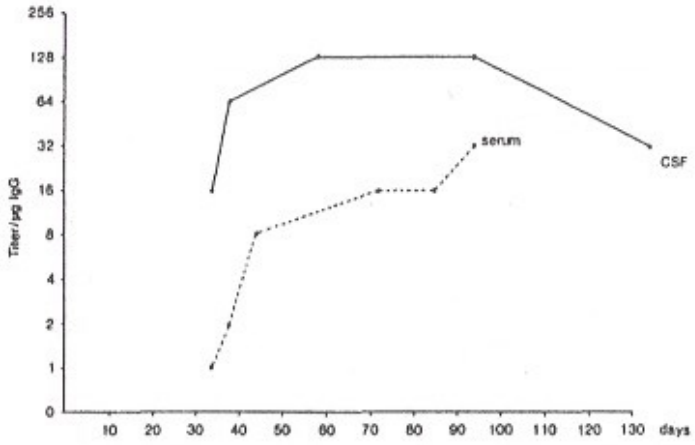
Figure 4 shows the titer per 1 µg IgG of every first serum/CSF-pair. The average difference of the binary dilution steps between serum and CSF was 2–3 over the course of 8 years. The low titer of 2 samples of a patient, whose disease was diagnosed after a delay of 12 years, was probably due to the Amoxycillin therapy two years ago. In our small collective it is impossible to decide whether the antibody response is influenced by antibiotic therapy.

Discussion

Because of the impermeability of the blood/CSF barrier locally synthesized antibodies in the nervous system can be demonstrated in the CSF, indicating activity of the corresponding antigen. Those antibodies can be easily demonstrated by comparing antibody titrations of aliquots of serum and CSF IgG.

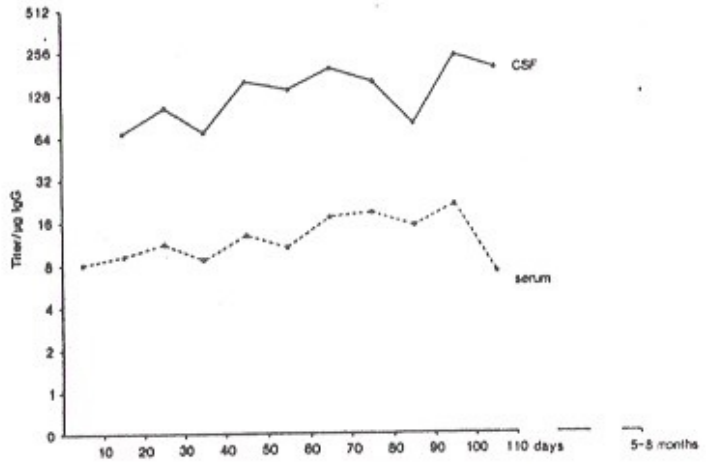
As expected all patients with the exception of 3 in the early stage of the disease with meningopolyneuritis (Garin-Bujadoux-Bannwarth) showed autochthonous borrelia antibodies in the CSF as did all patients with progressive borrelia encephalomyelitis. By this procedure the etiology of uncertain borrelia infections of the nervous system can be proven (1, 5).

Figure 1.



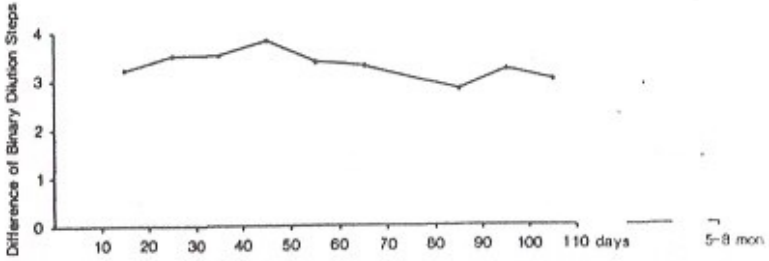
Antibodies to Borrelia burgdorferi per µg IgG in Serum and CSF in a 54 Years old Patient with Meningopolyneuritis Garin-Bujadoux, Bannwarth

Figure 2.



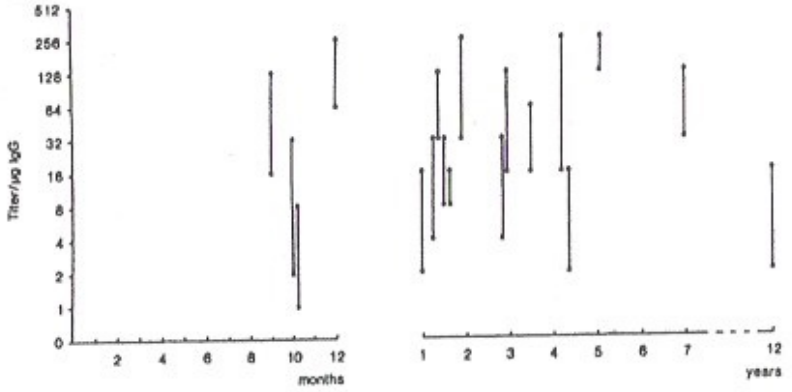
Average Values of Antibody Titers to Borrelia burgdorferi per µg IgG in 33 Patients with Meningopolyneuritis Garin-Bujadoux, Bannwarth

Figure 3.



Average Antibody Titers to Borrelia burgdorferi in Serum and CSF of 33 Patients with Meningopolyneuritis Garin-Bujadoux, Bannwarth

Figure 4.



Antibodies to Borrelia burgdorferi per µg IgG in Serum (•) and CSF (•) in 18 Patients with Progressive Borrelia Encephalomyelitis

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